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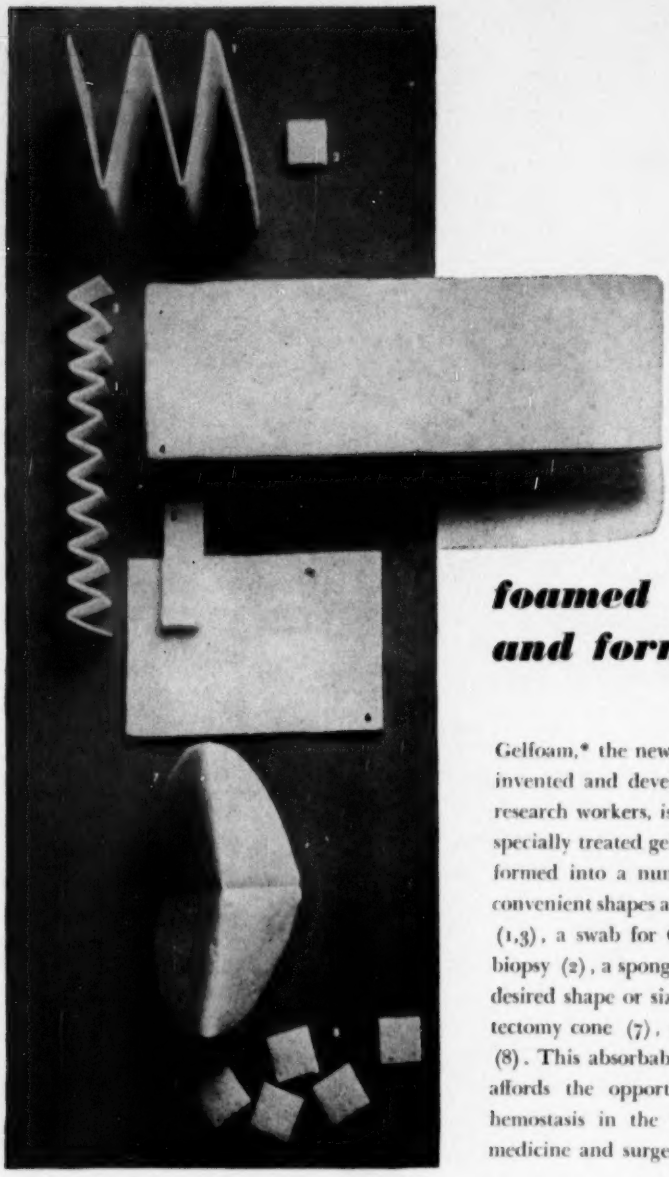
DECEMBER 1950
VOLUME 80 NUMBER 6

Published Monthly by
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Jan. 4, 1911, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $12.00



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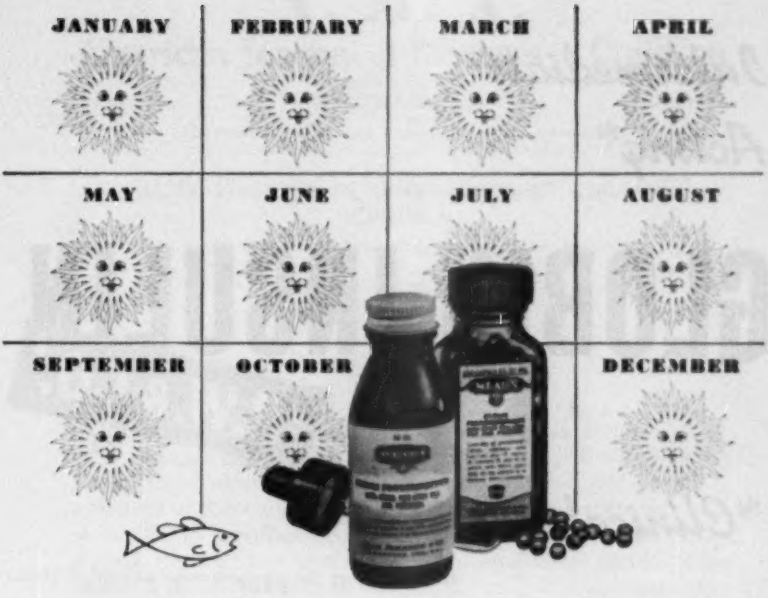

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1. *Rush, B. B., Rohr, J. R., and Colwell, A. R.: Proc. House Staff Dept. Med., Wesley Memorial Hospital, Chicago, Ill. Feb. 6, 1948.*

2. *Rohr, J. H., and Colwell, A. R., Proc. Amer. Diabetes Assn. 8:37, 1948.*

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LIVER STEATOSIS IN UNDERNOURISHED CHILEAN CHILDREN

I. Its Evolution as Followed by Serial Puncture Biopsies

JULIO MENEGHELLO, M.D.
HERMANN NIEMEYER, M.D.
AND
JULIO ESPINOSA, M.D.
SANTIAGO, CHILE

MALNUTRITION effects alterations of varying intensity in the organism of a child. These alterations are generally in direct relation to the intensity and type of the dietary deficiency and are usually looked for in those organs most accessible to clinical exploration, such as the skin, its appendages and the mucosa of the mouth or eyes. Some research workers [1] have been interested in morphological changes of the viscera in patients studied post mortem, but many of these changes, like fatty degeneration and cloudy swelling, cannot always be attributed to a deficient nutritional status. Instead, they may be the consequence of infections which commonly have been the immediate cause of death. However, little is known of the morphology of the internal organs in undernourished children during the reversible period, in which nutritional damage has not been sufficiently intense to bring about death. Thus, it was very important when the Gillmans [2] introduced the puncture biopsy technics for studying the livers of undernourished adults and children. The fundamental discovery made by the Gillmans was the demonstration in patients suffering from a pellagra-like disease of infants of the existence of an intense fatty infiltration of the liver as a

From the Hospital de Niños Manuel Arriarán and Cátedras de Pediatría of Prof. A. Baeza Goñi and J. Meneghello, Universidad de Chile.

1. Finkelstein, H.: Tratado de las enfermedades del niño de pecho, Madrid, Editorial Labor, 1932. Pfaundler, M. V., and Schlossmann, A.: Tratado enciclopédico de enfermedades de la infancia, Editorial Francisco Seix, Barcelona, 1934. Holt, L. E., and Howland, J.: Holt's Diseases of Infancy and Childhood: A Textbook for the Use of Students and Practitioners, ed. 11, New York, Appleton-Century Company, Inc., 1940.

2. Gillman, T., and Gillman, J.: A Modified Liver Aspiration Biopsy Apparatus and Technique, with Special Reference to Its Clinical Applications as Assessed by 500 Biopsies, South African J. M. Sc. **10**:53, 1945.

constant characteristic of the disease, appearing early and being independent of infectious complications. The Gillmans were able to follow the evolution of these fatty livers during the patients' hospitalization and to demonstrate that the amount of fat diminished as the clinical picture improved.

From their experience in 20 cases of "infantile pellagra," they were able to classify the hepatic alterations into three categories with regard to the amount of diffusely distributed fat, which was maximum in their first category, less in the second and slight in the third. Histological evolution beyond the third stage was not shown,[3] and in 19 of the 20 cases the condition was not followed beyond the second stage, in which the livers remained frankly fatty. The incompleteness of this observation attracted our attention.

After publication of the first papers of the Gillmans we decided to investigate the anatomic status of the liver in our dystrophic children. Having published a preliminary report,[4] we now present a more detailed description of the histological observations and a new classification, the result of our accumulated observations on a greater number of undernourished children. On this basis we will describe in this and subsequent papers the relation between the anatomic aspect of the liver, certain tests of its functions, and the effect of choline treatment.

MATERIAL AND RESULTS

This study was done on 92 children on whom 253 liver biopsies were performed during their hospital stay. The biopsies were done with the Silvermann needle, by the abdominal route and in accordance with technics the details and the relative safety of which have been previously described.[5] The subjects of the present communication showed no ill effects except for rare instances of transient gaseous distention. The children chosen corresponded to those whom Scroggie [6] has designated as having *distrofia policarencial*, a plurideficiency dystrophy in general similar to the "infantile pellagra" of South Africa and to conditions observed among undernourished children in several South American countries.[6] The infants, generally between the ages of 1 and 2½ years,

3. Gillman, T., and Gillman, J.: Hepatic Damage in Infantile Pellagra and Its Response to Vitamin, Liver and Dried Stomach Therapy as Determined by Repeated Liver Biopsies, J. A. M. A. **129**:12 (Sept. 1) 1945.

4. Meneghello, J.; Espinosa, J., and Coronel, L.: The Value of Liver Biopsy in Nutritional Dystrophia: Evaluation of the Treatment with Choline and Dried Stomach, Am. J. Dis. Child. **78**:141 (Aug.) 1949.

5. Meneghello, J.: Biopsia hepática: Análisis crítico de su importancia en clínica, Rev. chilena de pediat. **18**:322, 1947.

6. Scroggie, A.: Síndromes carenciales en la infancia, Rev. chilena de pediat. **12**:247, 1941.

enter the hospital with manifestly retarded height and weight, frequently with diarrhea and with a history of very deficient feeding, lacking principally in proteins and vitamins. A detailed clinical case, presented later in this paper, will best illustrate the character of this type of undernourishment.

In accordance with the histological appearances of the liver in these children, we have been able to group the morphological aspects into four stages, which have a certain similarity to the categories of the Gillmans.[3] The criteria chosen for classification are the amount of fat and the size of the fat drops. In the first stage staining with sudan III

Frequency of Some Histological Observations in Different Stages of Hepatic Steatosis *

Stage	1	2	3	4
Number of biopsies	56	38	37	33
Vacuoles 3+	44	5	..	..
Vacuoles 2+	11	31	5	1
Vacuoles 1+	..	..	14	6
Granular cytoplasm	13	25	28	23
Brown pigment	7	6	8	6
Biliary pigment	7	3	7	8
Sinusoids totally obliterated	10	1	1	..
Sinusoids partially obliterated	27	27	16	7
Sinusoids opened	19	10	20	26
Proliferation of Kupffer cells 3+	..	3	3	6
Proliferation of Kupffer cells 2+	3	7	4	6
Proliferation of Kupffer cells 1+	28	19	20	14
Proliferation of Kupffer cells ±	25	6	8	7
Cell infiltration of portal spaces 3+	4	5	8	4
Cell infiltration of portal spaces 2+	5	1	2	..
Cell infiltration of portal spaces 1+	18	9	12	7
Cell infiltration of portal spaces ±	29	22	15	22

* Staining was done by the hematoxylin and eosin method.

reveals the existence of fat in great quantities in the form of single large drops which fill the whole cell. In the second stage the liver shows a decrease in the amount of fat, which appears in the form of drops of all sizes. The third stage is characterized by the scarcity of fat, which appears principally in small droplets. In the fourth stage extremely few fat droplets may exist, generally of a small or medium size. In some livers of this group there is a predominance of a finely cloudy or granular appearance corresponding to the classic histological picture of cloudy swelling, while in the others the cytoplasm of all cells is homogenous and, indeed, appears as that of the normal liver.

In any of the stages of fatty infiltration and in the nonfatty livers a considerable amount of brown pigment may exist, causing the pathologist to conclude that there is pigmentary degeneration.

One must emphasize that the four stages do not correspond to histological pictures very clearly separated from one another; in many cases there are stages of transition which are difficult to catalog within the scheme. The relative difficulty becomes specially evident when one tries to differentiate between the first and second stages.

In the table are outlined in detail other characteristics of livers in the four stages of steatosis. Only the 164 biopsies performed on the last 63 children were used in making the table. The first cases were analyzed

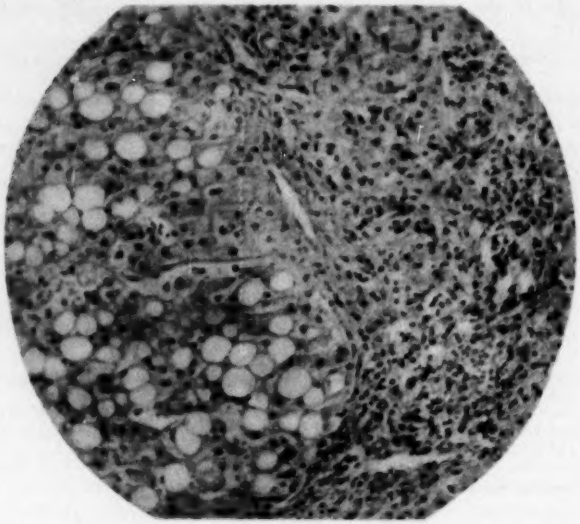

Fig. 1.—A hematoxylin-stained section showing vacuoles which correspond in quantity, size and position to the fat visible in the section stained specifically for fat.

in a previous communication,[4] and the results were very similar to those now shown.

In comparing a sudan III–stained section with one stained with hematoxylin, some vacuoles could be seen in the protoplasm of the latter (fig. 1) which corresponded in quantity, size and position to the fat visible in the section stained specifically for fat. Thus, for example, all livers in the first stage contained large vacuoles, which in 44 cases occupied almost every cell. On the other hand, in livers in the third stage these vacuoles were small and gave the cytoplasm a foamy aspect.

Another characteristic, which seemed important in the different stages of this classification, was the appearance of the sinusoids. In

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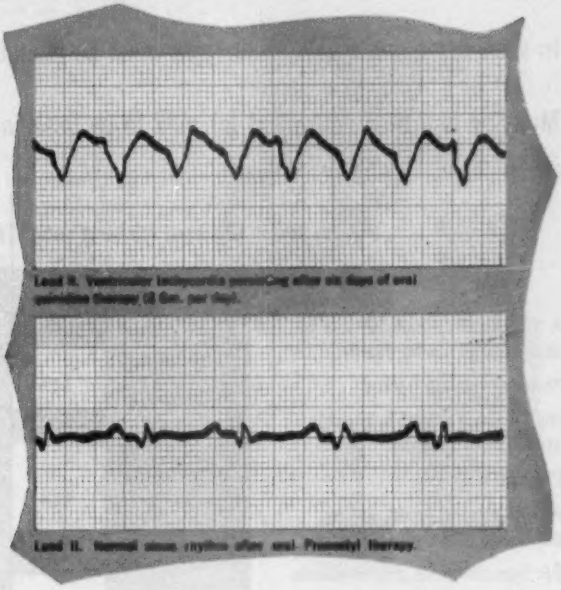

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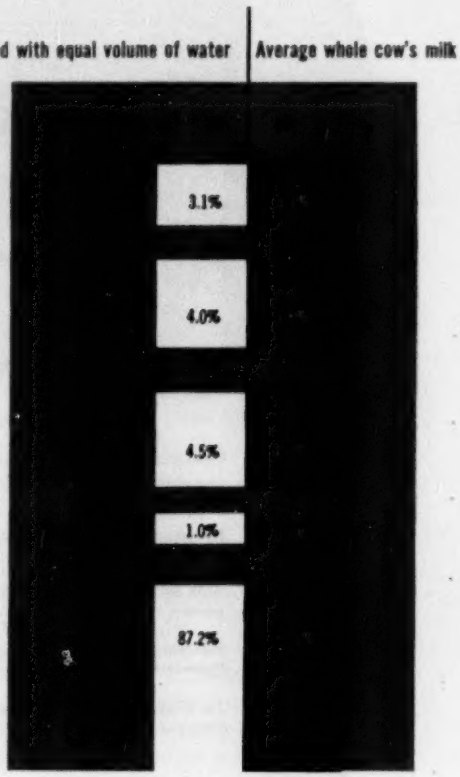

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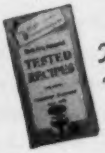
[1]Gamble, J. A.; Ellis, N. R. and Bailey, A. K., U. S. Dept. of Agric. Tech. Bull. No. 671, page 61, (March 1939).



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the first stage 17.9 per cent appeared completely closed, while, in contrast, only one (2.6 per cent) of the second stage, one (2.7 per cent) of the third stage and none of the nonfatty livers showed such a condition. In the last the sinusoids were frankly open and contained proportionately more red blood cells.

A slight increase in frequency and magnitude of Kupffer cell proliferation and in degree of mononuclear cell infiltration of portal spaces was seen in the livers in the third stage.

To discover what type of fat was present in the altered livers, chemical analyses were done [7] on the livers of 50 dystropic children who had died of various causes, including acute nutritional disorders, acute infections, chronic infections like tuberculosis and advanced stages of undernourishment. Among the last were some with plurideficiency dystrophy. The total lipids, phospholipids and cholesterol were measured within the first three hours after death. It was demonstrated that total lipids increased by as much as 20 per cent of total wet weight, but cholesterol, no more than 1 per cent. Phospholipids increased also, but when the amount of total lipids passed 11 per cent the quantity of phospholipids became stabilized at about 4 per cent. This shows that the majority of lipids accumulated were triglycerides. A comparison of the chemical measurements with the pathological information showed a close relation between them. The livers with brownish atrophy and those with cloudy swelling contained the lowest quantities of fat, while fatty livers contained the greatest amount in proportion to the intensity of fatty infiltration.

In nearly all children with plurideficiency dystrophy, livers in the first stage are found in biopsies done on admittance to the hospital. In a period of from 10 to 20 days one sees a partial disappearance of fat (the second stage), and in 20 to 30 days the fat has become reduced to fine droplets characteristic of the third stage. Many patients leave the hospital clinically well with the liver in this condition; but in others a normal histological condition of the liver is attained, preceded commonly by a stage of granular degeneration. The case now to be described shows the clinical course and evolution of hepatic steatosis.

REPORT OF A CASE

A 2 year old girl was admitted to the hospital on June 26, 1947, because of diarrhea for one month and bloody stools for one week. Up to the age of 8 months she was breast fed. At this time she began to receive a small amount of milk and gruel, soups, mashed potatoes and other vegetables. Meat, eggs, cheese, butter, fruits and vitamin supplements were never part of her diet. Since the age of 14 months she had not drunk any milk.

7. Niemeyer, H., and Iturra, T. S.: Estudios en el lactante distrófico. 2. Determinación post-mortem de los lípidos hepáticos, Rev. chilena de pediat. **18**:141, 1947.

Bouts of diarrhea and vomiting had occurred frequently in the past. The present attack, of four weeks' duration, had become steadily worse and with so much asthenia that walking, and even sitting up, were reported to have become impossible. There was edema of the legs and hands. Anorexia had been so marked that she had taken only weak black coffee during the previous two days. The history was otherwise noncontributory.

On examination at admission the child was very malnourished. Her weight was 15 pounds 12 ounces (7.14 Kg.) and her length 31.5 inches (80 cm.). She was apathetic, crying weakly and monotonously all the time. It was found that she could sit without help but was unable to stand, even when aided. The temperature was 98.6 F. (37 C.); the pulse (rate 120) was regular and soft, the blood pressure was 100/60 mm. Hg., and the respirations, 30 a minute.

The skin was pale, with generalized edema, particularly in the feet and legs. Elasticity of the abdominal wall was so decreased that thick persisting folds could be formed. On the trunk there was a fine, pigmented, scaling lesion caused by scratching alternating with areas of leukoderma, with areas of more marked pigmentation and of large scales posteriorly. The extremities were cool and

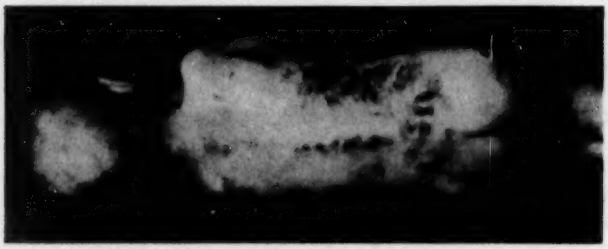

Fig. 2.—Fine, pigmented, scaling lesion on the trunk and ulcerative lesion at the level of the trochanter.

cyanotic, with a fine scaling on the extensor surfaces of the upper limbs and multiple ulcerative lesions on the lower, one of which, at the level of the trochanter, was particularly deep and 1.5 cm. in diameter (fig. 2). The skin of the feet and lower legs was reddish blue, shiny, wrinkled and hyperkeratotic.

The hair of the head was sparse and dry. There were impetigo of the scalp in the right parietal region and bleeding erosions due to scratching on the right ear and cheek.

The face was very pale and edematous. Examination of the eyes revealed blue scleras and very pale and dry conjunctivas. The child cried without tears. The pale, scaling lips were fissured, with bilateral cheilosis. Dentition was complete for a child of her age. The middle upper incisors showed loss of enamel; the gums were prominent and pale, and the wet, light red tongue was smooth in the center.

Examination of the thorax revealed bony prominences with a scorbutic rosary, clear lungs and normal heart sounds. The abdomen was soft; the liver palpable 0.5 cm. below the costal margin, and the spleen, nonpalpable.

There was hypotonicity of the extremities with muscular atrophy, but otherwise the physical examination was noncontributory.

The blood count showed 3,640,000 red cells and hemoglobin level of 10.1 Gm. There were 1 per cent reticulocytes. The cell volume was 97 cubic microns. White cells numbered 12,800, of which 50 per cent were segmented (polymorphonuclear) granulocytes (11 per cent stab cells), 46 per cent lymphocytes, 2 per cent monocytes and 2 per cent Türk cells. Thrombocytes (platelets) were slightly decreased. There was anisocytosis with moderate macrocytosis (some of the macrocytes were polychromatophilic), but the leukocytes were normal.

Myelograms showed a bone marrow of good density; 240,000 cells per cubic millimeter, a diminished erythroblastic series (11.2 per cent), with a discrete normochromic anisocytosis, and granulocytic series very slightly increased (55.7 per cent). When the slides were reviewed, granular and nongranular megakaryocytes in greater than normal proportions were found.

Prothrombin time and bleeding and clotting times were normal.

The total serum proteins were 3 Gm. per 100 cc.; ascorbic acid, 0.16 mg. per 100 cc. of plasma and the Kajdi index,[8] 0.80.

The cephalin-cholesterol and Takata-Ara reactions were 2 +; the urine was normal; stool examination showed no red or white blood cells, pathogenic organisms on culture or parasitic ova.

Examination of eye scrapings for vitamin A deficiency[9] gave positive results. Examination of the gastric juice revealed a total acidity equivalent to 15 cc. of N/10 sodium hydroxide per 100 cc. of gastric juice.

Roentgen examination of the long bones showed discrete osteoporosis, a thinned bone cortex, a slight intensification of the line of temporary calcification and a small area of bone rarefaction in both angles of the distal extremity of the radius and proximal extremity of the tibia. From these characteristics osteal alterations diagnosis of a prescorbutic condition was made.

Treatment with sulfathiazole was instituted because the child's history indicated possible intestinal infection, but it was discontinued after four days when the stools became normal after a two day period of constipation. Two hundred and fifty milligrams of vitamin C was given daily for five days. The child also received hydrochloric acid therapy for 15 days. Apart from this, the treatment was entirely dietary. The child's tolerance for food was so good that after a 12 day curative diet of protein milk, a change could gradually be made to a complete diet including powdered whole milk, vegetables, leguminous purées, eggs, butter, fried potatoes and fruit.

The child remained apathetic during the first nine days of therapy but took food well. The edema disappeared slowly, persisting to a slight degree for nearly a month. The skin alterations diminished in intensity within two weeks, but slight manifestations of hyperkeratosis and melanosis persisted until the end of the second month. After 17 days purpuric lesions, which had appeared on the third day, disappeared. The mucous membranes improved between the second and third weeks, with a disappearance of dryness of the conjunctivas and of cheilosis, but improvement of the tongue took somewhat longer. During the second month the child's spirits were definitely improved and she began to walk with support. She gained weight steadily from the twelfth day and reached 19 pounds 13 ounces (9 Kg.) by the sixty-fifth day, when she was discharged from

8. Kajdi, L.; Light, J., and Kajdi, C.: Test for Determination of Vitamin C Storage, J. Pediat. **15**:197, 1939.

9. Maffioletti, F.: Hipovitaminosis A en el lactante: Test de queratinización de la conjunctiva, Thesis, Santiago, University of Chile, 1945.

the hospital. During the course of her illness two complications arose: an abscess of the left thigh and paronychia of the left thumb. Both of these were rapidly cured with penicillin.

Control laboratory examinations showed gradual improvement of most of the alterations. The marrow persisted in showing total hypoplasia of the erythroblastic series, which manifested itself in a mild anemia, treated by repeated red cell transfusions. The flocculation tests remained altered, while the serum proteins increased to a level of 6.8 Gm. per 100 cc. in two months.

During the child's hospital stay four liver biopsies were performed. The first, 10 days after admission, revealed the liver to be in the first stage of fatty infiltration. At 23 days the results of another biopsy showed the liver to be in the second stage with perilobular distribution of the fat. The third and fourth biopsies, done on the thirty-sixth and sixty-fourth days of hospitalization, both showed the liver to be in the third stage. She was discharged on the sixty-fifth day.

COMMENT

We have supposed liver steatosis to result from an excessive transformation of carbohydrates to lipids and a decreased removal of these lipids from the liver because of the lack of some lipotropic agents.[10] This supposition is based on dietary histories of our patients, who ate excessive amounts of carbohydrate and almost no proteins, and on the physiopathological data from experimentally obtained fatty changes.

Proliferation of Kupffer cells and monocytic infiltration of the portal spaces are some evidence that fat may be removed, like foreign bodies, by phagocytes. In contrast to observations of Davies[11] is the curious fact that in many of our histological preparations the disappearance of fat begins by fragmentation of large drops in the central region of the lobule, the area in which cells free from fat first appear. This may suggest the possibility of removal via the centrolobular vein. In the second stage of steatosis fat predominates in peripheral cells of the lobules, where the amount of fat is usually greater and the drops larger than centrally.

The exact significance of the intracellular granules of brown pigment is not known, nor is that of the biliary pigments in the cells, since they are almost never associated with hyperbilirubinemia.

It is very difficult to establish the clinical importance of fatty infiltration of the liver. Although, in general, there is a relation between the bad condition in which the child enters the hospital and the degree of fatty infiltration, a liver with first stage steatosis is sometimes found in patients of quite satisfactory general state. Since it is commonly observed

10. Meneghello, J., and Niemeyer, H.: Alteraciones hepáticas en el lactante desnutrido, Second Meeting of the Confederation of South American Pediatric Societies, Buenos Aires, 1949. Meneghello, J.: Desnutrición en el lactante mayor, Santiago, Chile, Central de Publicaciones, 1949.

11. Davies, J. N. P.: The Essential Pathology of Kwashiorkor, Lancet, 1:317, 1948.

after about 15 days that the child is doing well and the weight rising, though the liver is still intensely fatty, clinical progress appears to be more rapid than loss of liver fat. In view of this, we believe a pronounced degree of fatty infiltration need not always be linked with a bad prognosis. Gillman and co-workers,[3] Waterlow [12] and Magalhães Carvalho [13] stated the belief, however, that the gravity of the disease in their patients and the survival prognosis depend fundamentally on the amount of fat in the liver, and they reported high mortality. The degree of fatty infiltration of the liver in our hospitalized children is as great as in those of the South African, Brazilian and West Indian children, but the mortality rate for our patients is, in contrast, lower by about 8 per cent.

The question of association with cirrhosis is obviously important. Waterlow [12] has frequently found an increase of reticulin of the liver in patients with what he has called "fatty liver disease," and Gillman and Gillman [14] have shown a sequence of change from the fatty livers of early stages of pellagra to the pigmentary cirrhosis of advanced stages. This problem is now arousing great interest and has been extensively discussed by Himsworth.[15]

SUMMARY

The histologic changes of the liver in plurideficiency dystrophy were studied by means of 164 puncture biopsies in 63 children, practically all of them between 12 and 30 months of age.

The existence of an intense fatty infiltration which disappears slowly in about two months of hospital care was proved.

Four stages of fatty infiltration are described, the first corresponding to a maximal steatosis and the fourth to a nonfatty liver. Other histological aspects of the liver are noted.

The quality of the fat deposited, its origin and clinical significance for the patients are briefly analyzed.

Dr. Clement A. Smith, of Harvard University, gave advice during the preparation of the manuscript.

12. Waterlow, J. C.: Fatty Liver Disease in Infants in the British West Indies, Medical Research Council, Special Report Series, no. 263, London, His Majesty's Stationery Office, 1948.

13. de Magalhães Carvalho, J.: Contribuição ao tratamento da distrofia pluricarencial hidropigênica, Hospital, Rio de Janeiro, **32**:307, 1947.

14. Gillman, J., and Gillman, T.: Structure of the Liver in Pellagra, Arch. Path. **40**:239 (Oct.) 1945.

15. Himsworth, H. P.: Lectures on the Liver and Its Diseases, Comprising the Lowell Lectures Delivered at Boston, Massachusetts, March 1947, Oxford, Basil Blackwell & Mott, Ltd., 1948.

LIVER STEATOSIS IN UNDERNOURISHED CHILEAN CHILDREN

II. Study on Some Liver Function Tests

HERMANN NIEMEYER, M.D.
AND
JULIO MENEGHELLO, M.D.
SANTIAGO, CHILE

AFTER it became known that various dietetic modifications could produce fatty infiltration of the liver, several investigators attempted to determine the effect, if any, of the infiltration on liver function. MacLean, Ridout and Best [1] found impairment of sulfobromophthalein sodium excretion in 50 per cent of experimental rats with prolonged liver steatosis. McKibbin and co-workers [2] demonstrated in dogs with fatty livers an alteration of the phosphatase of the blood, a deficiency in the excretion of sulfobromophthalein sodium, a prolonged prothrombin time and a reduction in the total cholesterol and in the ester ratio. The results of the colloidal gold test remained normal. Li and co-workers,[3] also working with dogs, found an impairment in the excretion of bengal rose and a great susceptibility to chronic poisoning with benzene.

In studies on human beings there have also been attempts to correlate fatty infiltration of the liver accompanying various diseases with results of some of the usual tests of hepatic function. Franklin and co-workers [4] studied, by means of puncture biopsies, the fatty livers of

From the Hospital de Niños Manuel Arriarán and Cátedras de Pediatría of Prof. A. Baeza Goñi and J. Meneghello, Universidad de Chile.

1. MacLean, D. L.; Ridout, J. H., and Best, C. H.: Effects of Diets Low in Choline upon Liver Function, Growth and Distribution of Fat in White Rat, Brit. J. Exper. Path. **18**:345, 1937.

2. McKibbin, J. M.; Thayer, B. A., and Stare, F. J.: Choline Deficiency Studies in Dogs, J. Lab. & Clin. Med. **29**:1109, 1944. McKibbin, J. M.; Ferry, R. M.; Thayer, B. A.; Patterson, E. G., and Stare, F. J.: Further Studies on Choline Deficiency in Dogs, ibid. **30**:422, 1945.

3. Li, T. W., and Freeman, S.: Effect of Protein Deficiency and Cholesterol Feeding on the Liver of Dogs, Am. J. Physiol. **145**:646, 1946. Li, T. W.; Freeman, S.; Hough, V. H., and Gunn, F. D.: The Increased Susceptibility of Protein-Deficient Dogs to Benzene Poisoning, ibid. **145**:166, 1945.

4. Franklin, M.; Salk, M. R.; Steigmann, F., and Popper, H.: Clinical, Functional and Histological Responses of Fatty Metamorphosis of Human Liver to Lipotropic Therapy, Am. J. Clin. Path. **18**:273, 1948.

five patients with nutritional disorders and found that there were neither symptoms of hepatic disease nor any constant alteration of the results of function tests. Three of their patients had normal thymol turbidity reactions; four had impairment of sulfobromophthalein sodium excretion, and all five had no abnormality of prothrombin time, bilirubin level or cephalin-cholesterol flocculation reaction. In a subsequent paper, Franklin and co-workers [5] compared the histological appearance of the liver with many laboratory findings and found no correlation between the intensity of fatty infiltration and the alteration of the results of any flocculation tests. Gillman and Gillman [6] found, in children with "infantile pellagra," that flocculation tests, such as the Takata-Ara, colloidal gold and cephalin-cholesterol, did not reflect the considerable alterations in hepatic cells, consisting principally of a great infiltration of fat. Waterlow,[7] on the other hand, stated that the excretion of sulfobromophthalein sodium is definitely diminished in children with intense fatty infiltration of the liver of nutritional origin. Delgado [8] has shown that dystrophic Chilean infants exhibit an abnormal excretion of hippuric acid and that the results of Takata-Ara and Hanger tests are frequently positive. Later, Meneghello and co-workers [9] compared the results of these flocculation tests with the histological picture of the liver as seen by biopsies and found no strict correlation between modification of the results of the tests and amount of liver fat.

Because of this general lack of agreement between results of flocculation tests and degree of hepatic steatosis, an attempt was made to correlate these two factors in another group of Chilean children with a nutritional disorder involving extreme fatty infiltration of the liver. The majority of the children studied were suffering from "plurideficiency dystrophy," the principal characteristics of which have been defined in earlier papers.[10]

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5. Franklin, M.; Popper, H.; Steigmann, F., and Kozoll, D.: Relation Between Structural and Functional Alterations of the Liver, J. Lab. & Clin. Med. **33**:435, 1948.

6. Gillman, T., and Gillman, J.: A Modified Liver Aspiration Biopsy Apparatus and Technique, with Special Reference to Its Clinical Applications as Assessed by 500 Biopsies, South African J. M. Sc. **10**:53, 1945.

7. Waterlow, J. C.: Fatty Liver Disease in Infants in the British West Indies, Medical Research Council, Special Report Series, no. 263, London, His Majesty's Stationery Office, 1948.

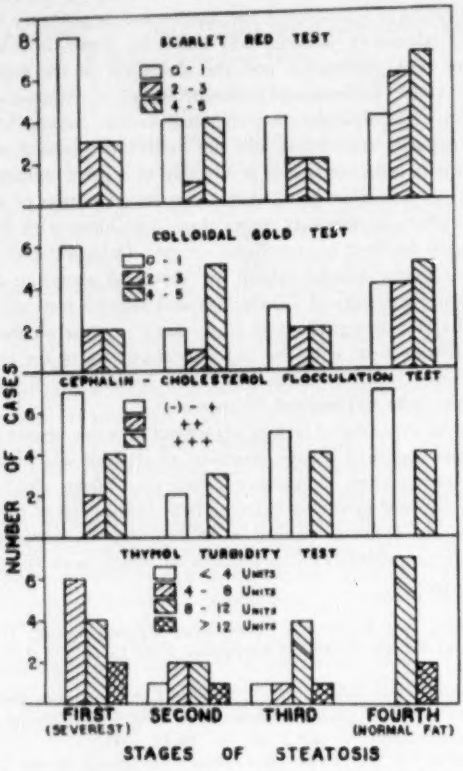
8. Delgado, G.: Insuficiencia hepática en el lactante distrófico, Thesis, Santiago, University of Chile, 1945.

9. Meneghello, J.; Espinosa, J., and Coronel, L.: The Value of Liver Biopsy in Nutritional Distrophia: Evaluation of the Treatment with Choline and Dried Stomach, Am. J. Dis. Child. **78**:141 (Aug.) 1949.

10. Meneghello, J.; Niemeyer, H., and Espinosa, J.: Liver Steatosis in Undernourished Chilean Children: I. Its Evolution as Followed by Serial Puncture Biopsies, Am. J. Dis. Child., this issue, p. 719. Footnote 9.

MATERIAL AND RESULTS

Our results were obtained from 31 patients whose original biopsies showed some degree of hepatic steatosis. The original and later biopsies, totaling 53, were accompanied with simultaneously performed flocculation tests. In certain cases carbohydrate tolerance tests were also done.



Relation of results of four liver function tests to degree of steatosis.

The flocculation tests gave positive results in almost 75 per cent of the cases, varying in intensity from minimal to maximal flocculation. In the chart appear the results of the colloidal gold, scarlet red, thymol turbidity and cephalin-cholesterol tests. The colloidal gold was prepared according to the method of Maclagan.[11] The scarlet red test corresponded

11. Maclagan, N. F.: Serum Colloidal Gold Reaction as Liver Function Test, Brit. J. Exper. Path. **25**:15, 1944.

to the test described by Ducci.[12] Thymol turbidity was read in an Evelyn photocolorimeter with a copper sulfate standard, as recommended by Ducci.[13] Difco brand cephalin-cholesterol was used. In most of the cases all four tests were made with the same sample of serum. As the chart indicates, either normal or abnormal flocculation reactions may accompany any one of the four stages of steatosis, from maximal fatty infiltration of the liver (first stage) to absence of abnormal fat (fourth stage). Alteration in flocculation may reach the highest degree found in infectious hepatitis. The results suggest, but by no means prove, a negative correlation between degree of fatty infiltration and amount of flocculation.

In 15 cases it was possible to follow in the same children the evolution of both the test results and histological changes in the liver. The results are presented in table 1. In 10 of these cases the test results continued to be without important modifications during the entire time that the infant was hospitalized, while the abnormal fat was being removed. In

TABLE 1.—*Repeated Flocculation Tests on Fifteen Patients Showing About the Same Rate of Removal of Liver Fat by Repeated Biopsies*

Number of Patients	Change in Intensity of Flocculation
1	Decreased
4	Increased
4	Repeatedly — or + flocculation
6	Repeatedly ++ or +++ flocculation

some of the 10 cases flocculation reactions were negative or slightly positive, and in others they were frankly positive. In four the reactions became more strongly positive, despite restitution of the histologic condition of the liver to normal.

No correlation was observed between results of flocculation tests and clinical findings.

In 12 dystrophic infants we were able to perform simultaneously carbohydrate tolerance tests and puncture biopsies of the liver. The tests were performed by administering intravenously a 50 per cent solution of dextrose or galactose, in a dose of 1 or 2 cc. per kilogram of body weight, the dextrose test being done first and followed on the next day by the galactose test. The tests were evaluated by the formula of Colcher and co-workers [14] for disappearance from the blood of intravenously

12. Ducci, H.: Colloidal Red Test for Study of Hepatic Dysfunction, J. Lab. & Clin. Med. **32**:1273, 1947.

13. Ducci, H.: Thymol Test of Maclagan: Standardization and Adaptation to Evelyn Photoelectric Colorimeter, J. Lab. & Clin. Med. **32**:1273, 1947.

14. Colcher, H.; Patek, A. J., Jr., and Kendall, F. E.: Galactose Disappearance from the Blood Stream: Calculation of a Galactose Removal Constant and Its Application as a Test for Liver Function, J. Clin. Investigation **25**:768,1946.

administered galactose. In a large number of such tests Niemeyer and Valencia [15] showed that disappearance of galactose and dextrose from the blood of normal and of ill children may be expressed by a single standard formula. This formula defines a constant (K) which represents the percentage of blood sugar concentration removed from the circulatory stream each minute. The minimal normal value for the dextrose removal constant (K dextrose) was 2.56, and for the galactose removal constant (K galactose), 2.70. Values below these indicate a decreased tolerance to the particular carbohydrate.

The results are shown in table 2. In some of these undernourished children a decreased carbohydrate tolerance appeared, sometimes to one sugar and sometimes to both dextrose and galactose, but without a

TABLE 2.—*Relation Between the Intravenous Dextrose and Galactose Tolerance Tests and the Stage of Liver Steatosis in Twelve Children* *

Stage of Liver Steatosis	K Dextrose	K Galactose
1	8.32	....
1	7.16	4.15
1	1.30	2.17
2	3.67	3.94
2	2.06	3.28
2	0.96	5.61
3	4.72	5.70
3	4.08	2.67
4	3.96	3.55
4	3.04	5.42
4	2.16	4.08
4	1.89	4.49

* Values above a line indicate a decreased tolerance to the particular carbohydrate.

definitive relation between the fat content of the liver and the carbohydrate tests. Some children with a very fatty liver (as in the first and second stages of steatosis) presented a normal response to the administration of carbohydrates. On the other hand, some with livers which appeared normal on histological examination had impaired tolerance test results. Special staining for glycogen has not yet yielded significant results.

The obvious disagreement between the results of one sugar test and those of the other will be discussed below.

COMMENT

Although flocculation tests are often considered helpful in the differential diagnosis of hepatobiliary diseases and, more precisely, in the

15. Niemeyer, H., and Valencia, S., A.: Pruebas intravenosas de tolerancia a los hidratos de carbono en el niño, Rev. chilena de pediat. **20**:267, 1949.

differentiation of icteric syndromes,[16] the flocculation tests also elicit positive reactions in several diseases in which there is no direct involvement of the liver.[17] Since these tests depend essentially on an alteration in the relative proportion of different serum proteins and on their qualitative modification,[18] any factor which effects these changes in the serum proteins may produce a positive reaction in the flocculation test.

In these undernourished children there was usually a hypoproteinemia, with a fall in the albumin fraction and sometimes an elevation of the globulins.[19] The question arises whether these changes (and the corresponding disturbances of flocculation test results) were produced by the protein-deficient diet or were determined by a relative incapacity of the liver to synthesize serum albumin. Although the problem cannot be solved with present information, the practical consequence is that the pediatrician must be extremely cautious in interpreting results of so-called hepatic function tests (flocculation type) on an icteric infant or young child with poor nutrition.

In respect to carbohydrate tolerance tests the results agree with those obtained in a larger group of undernourished children in which there was observed a tendency toward a low tolerance to intravenously administered galactose and dextrose.[15] The degree of fatty infiltration of the liver seems not to affect the results in any special way. Tisdall and co-workers [20] found that the undernourished infant removes injected dextrose from the blood stream with the same rapidity as the normal infant. However, more recently, Holmes and Trowell [21] have reported from Africa a diminished tolerance to injected dextrose in undernourished patients. These authors also studied the amount of glycogen deposited in the liver after the administration of dextrose and demonstrated failure of deposition in undernourished children as compared

16. Maclagan, N. F.: Liver Function Test in the Diagnosis of Jaundice: A Review of 200 Cases, Brit. M. J. **2**:197, 1947. Alessandri, H.; Ducci, H., and Roeschmann, W.: Contribución del laboratorio al diagnóstico diferencial de las ictericias, Rev. méd. de Chile, **75**:151, 1947. Armas-Cruz, R.; Montero, E.; Cabello, J.; Lobo-Parga, G., and Dávila, M.: Contribución del laboratorio al diagnóstico diferencial de las ictericias, ibid. **75**:157, 1947.

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20. Tisdall, F. F.; Drake, T. G. H., and Brown, A.: The Carbohydrate Metabolism of the Marantic Infant, Am. J. Dis. Child. **30**:829 (Dec.) 1925.

21. Holmes, E. G., and Trowell, H. C.: Formation of Hepatic Glycogen in Normal Africans and in Those Suffering from Malignant Malnutrition, Lancet **1**: 395, 1948.

with that of four controls in a good state of nutrition. That we often found a normal tolerance to galactose with a low tolerance to dextrose suggests the possibility of other factors, such as endocrine influences, which act on dextrose metabolism but not on galactose assimilation. This problem will be the subject of subsequent studies in undernourished children.

SUMMARY

Fifty-three puncture biopsies of the liver were performed in 31 undernourished children simultaneously with several flocculation tests (colloidal gold, scarlet red, thymol turbidity and cephalin-cholesterol).

It was apparent that either normal or abnormal results of flocculation tests might accompany any types of liver steatosis observed. There was a tendency toward a negative correlation between the degree of fatty infiltration and the amount of flocculation.

In 15 cases it was possible to follow in the same children the evolution of both the results of the tests and the histological changes of the liver. It was shown that while the amount of liver fat was decreasing, the intensity of flocculation might decrease, increase or remain unchanged.

In 12 children on whom intravenous carbohydrate tolerance tests and biopsy of the liver were simultaneously performed, the results of one or both carbohydrate tests were abnormal. However, in six there was no definitive correlation between the fat content of the liver and tolerance to carbohydrates.

The significance of these findings is briefly discussed.

Dr. Clement A. Smith, of Harvard University, gave advice during the preparation of the manuscript.

LIVER STEATOSIS IN UNDERNOURISHED CHILEAN CHILDREN

III. Evaluation of Choline Treatment with Repeated Liver Biopsies

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AND
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AS A RESULT of advances in knowledge of fat metabolism and of conditions producing abnormal fat deposits in the liver, the treatment of such conditions has aroused great medical interest. In experimental animals it is possible to produce by dietary modifications two principal types of liver change, fatty infiltration and massive acute necrosis,[1] and both of these may lead to cirrhotic alterations. The first type may be prevented in experimental animals by so-called lipotropic agents, such as choline and methionine; the second, by cystine.[1]

This knowledge was soon applied clinically. After publication of Patek's work,[2] the advantage of providing diets rich in proteins and carbohydrates, relatively poor in fats and supplemented with vitamins was universally accepted in the treatment of liver diseases. Several groups of investigators [3] then began to use lipotropic agents, especially for patients with cirrhosis of the liver and varying degrees of fatty infiltration. Results have been contradictory and their interpretation difficult. Although the general impression is that addition of such ther-

From the Hospital de Niños Manuel Arriarán and Cátedras de Pediatría of Prof. A. Baeza Goñi and J. Meneghello, Universidad de Chile.

1. Himsworth, H. P.: Lectures on the Liver and Its Diseases, Comprising the Lectures Delivered at Boston, Massachusetts, in March 1947, Oxford, Basil Blackwell & Motto, Ltd., 1948.

2. Patek, A. J., Jr.: Treatment of Alcoholic Cirrhosis of the Liver with High Vitamin Therapy, Proc. Soc. Exper. Biol. & Med. **37**:329, 1937.

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apeutic agents to the diet produces clinical improvement, failures have also been reported.[4] Weir [5] has made a critical analysis of these reports and blamed the uncertainty of their conclusions on the diverse criteria used to evaluate results and on lack of adequate controls.

Hoagland and Shank [6] found lipotropic agents ineffective in cases of infectious hepatitis, but in cases of toxic hepatitis results have been more encouraging.[7]

By the puncture biopsy technic Franklin and co-workers [8] studied the fatty livers of 10 patients with cirrhosis and five patients with nutritional disorders. In some cases they repeated the biopsy after two to four weeks of treatment with protein-rich diets supplemented with lipotropic agents. These authors found that the general condition and the results of liver function tests had improved in all their patients while the livers had simultaneously become defatted. On the other hand, Magalhães Carvalho [9] stated that he did not recommend the use of choline in treating fatty livers of patients with what he calls *distrofia pluricarencial hidropigênica*, a disease similar to what we call plurideficiency dystrophy. However, he used only small amounts of the substance and evaluated results only by mortality rate, which may be influenced by many conditions.

After publication of the reports of Gillman and others [10] we tested the effect of desiccated pig stomach and of choline on the fatty livers found in our children with plurideficiency dystrophy. In preliminary studies Meneghello and co-workers [11] did not find any important action of these substances on the defatting of livers. Since then we have had more experience with choline and shall now present the results.

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4. Yater, W. M., in discussion on Greene, C. H.: Physiologic Considerations in the Treatment of Portal Cirrhosis, J. A. M. A. **121**:715 (March 6) 1943. Man, E. B.; Kartin, B. L.; Durlacher, S. H., and Peters, J. P.: Lipids of Serum and Liver in Patients with Hepatic Diseases, J. Clin. Investigation **24**:623, 1945.

5. Weir, J. F.: Modern Physiologic Concepts: Their Application to the Treatment of Diseases of the Liver, J. A. M. A. **134**:579 (June 14) 1947.

6. Hoagland, C. L., and Shank, R. E.: Infectious Hepatitis: A Review of 200 Cases, J. A. M. A. **130**:615 (March 9) 1946.

7. Eddy, J. H., Jr.: Methionine in the Treatment of Toxic Hepatitis, Am. J. M. Sc. **210**:374, 1945.

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9. de Magalhães Carvalho, J.: Contribuição ao tratamento da distrofia pluricarencial hidropigênica, Hospital, Rio de Janeiro, **32**:307, 1947.

10. Gillman, T.; Gillman, J.; Inglis, J.; Friedlander, L., and Hammar, E.: The Substitution of Whole Stomach Extract for Vitamins in the Treatment of Malignant Infantile Pellagra, Nature, London, **154**:210, 1944.

11. Meneghello, J.; Espinosa, J., and Coronel, L.: The Value of Liver Biopsy in Nutritional Dystrophia: Evaluation of the Tre-tment with Choline and Dried Stomach, Am. J. Dis. Child. **78**:141 (Aug.) 1949.

MATERIAL AND RESULTS

We have studied a group of 41 comparable children. They belonged to the same age group; their dietary deficiencies were similar, and their clinical symptoms showed little variation. All underwent liver biopsy shortly after admission, and histological examination of the tissue revealed marked fatty infiltration corresponding to what we have called the first, and severest, stage of liver steatosis.[12] We have not included in this paper a large number of cases in which the histological condition of the liver was not investigated on admission or other cases in which the liver was already in the second or third stage when the children were hospitalized. Each patient had two to eight biopsies, thus

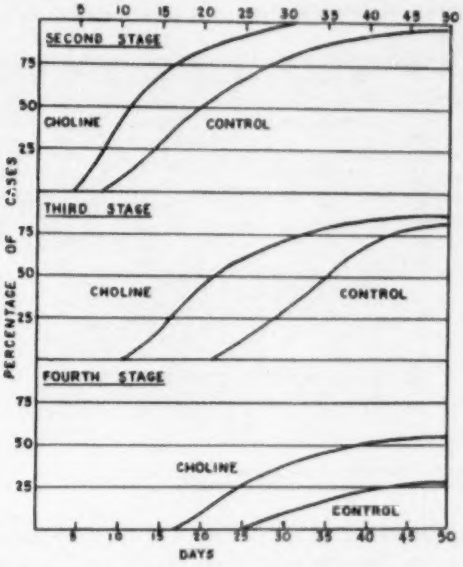

Chart 1.—Days on which biopsies were done and stages of fatty infiltration.

allowing us to follow histological liver changes and to check important alterations in relatively short periods. Data from cases not followed regularly were discarded. All patients were given a regular diet of protein milk (high protein, partially skimmed and acidified), an adequate amount of carbohydrate and other foods acceptable to the children, such as soups, meat and eggs. At least during the first two or three weeks they received daily approximately 3.5 Gm. of milk protein and 2.5 Gm. of fat per kilogram of body weight. Frequently blood transfusions were given, according to individual need. From the 41 children, 23 unselected

12. Meneghello, J.; Niemeyer, H., and Espinosa, J.: Liver Steatosis in Undernourished Chilean Children: I. Its Evolution as Followed by Serial Puncture Biopsies, Am. J. Dis. Child., this issue, p. 719.

ones were treated with choline.[13] The other 18, used as controls, showed the same severity of nutritional damage. Choline hydrochloride was given orally as soon as the patients were admitted, the daily dose being 25 cc. of a 20 per cent solution, for at least 10 days, with several patients receiving this medication for 20 days or more.

Chart 1 shows the days on which biopsies were done and the stages of fatty infiltration according to our classification. When two successive biopsies showed a shift from one stage to the next, we selected the midpoint of the period between the two biopsies as the hypothetical moment when the histological change occurred. When the shift in two successive biopsies was from one stage to the second after it, the time elapsed between the two was divided into three periods and the middle one of these periods selected as the time when the liver was going through the undetected stage.

Histological Evolution of Livers that were Previously in First Stage of Steatosis: Influence of Choline Treatment

Following Stage	Time, Days	Without Treatment		With Choline		$\frac{M_1 - M_2}{S.\ D.\ Diff.}$*
		No.	Per Cent	No.	Per Cent	
		(18)†		(23)		
2	10	1	5.6	11	47.8	2.95
	20	9	50.0	19	82.6	2.21
	30	15	83.4	22	95.6	1.31
	40	16	89.0	23	100.0	1.63
	50	16	89.0	23	100.0	1.63
		(18)		(22)		
3	20	0	0	10	45.5	3.31
	30	5	27.8	15	68.1	2.54
	40	13	72.2	18	81.9	1.48
	50	14	77.6	19	86.4	1.0
		(13)		(16)		
4	20	1	7.7	6	37.5	1.86
	40	3	23.1	8	50.0	1.49
	50	4	30.8	9	56.2	1.37

* The difference is significant if this quotient is 2 or more.
† Figures in parentheses are the number of patients.

The table shows that the administration of choline apparently accelerated loss of liver fat, although the final result was the same with or without such treatment. Thus, the percentage of children whose livers changed from the first to the second stage of steatosis before 10 and 20 days was significantly higher in the treated group. Only 5.6 per cent of the controls, as compared with 47.8 per cent of those receiving choline, reached the second stage in 10 days; for 20 days these figures are 50.0 per cent and 82.6 per cent respectively. In the shift to the third stage the same tendency is seen, with a significantly higher percentage of the treated patients changing in 30 days and, again, a similarity in the later figures for the two groups. When the percentages of patients reaching

13. Dr. Héctor Croxatto, of Instituto M. T. Sanitas y Anilinas S. A., supplied the choline chloride.

the fourth stage are considered, a difference in favor of the treated group is also found, but the number of patients followed to this stage is too small to give significant results.

In chart 2 are shown the percentages of children in the various stages of liver steatosis at any period of hospitalization. Initially, all these infants' livers were in the first stage. From the graph it is possible to see that the percentages of treated patients attaining the less fatty stage are consistently higher than those of the control group, although as time passes both percentages tend to become alike. The effect of choline therapy is thus one of more rapid improvement rather than degree of ultimate improvement achieved.

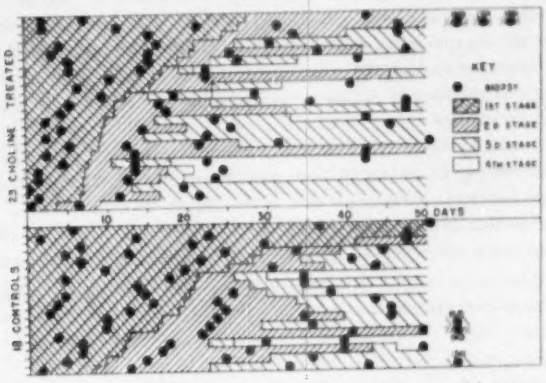

Chart 2.—Percentage of patients reaching successive stage of improvement.

COMMENT

We believe our results interesting because they come from a controlled group of patients studied by a method which measures changes in amounts of fat accumulated in the cells and which thus directly evaluates lipotropic activity.

The animal studies referred to above [1] have shown choline to be less effective in therapy than in prophylaxis of liver steatosis. Therefore an immediate and complete therapeutic response in human patients is perhaps not to be expected.

We believe it important that with choline administration there is an acceleration of change from the very fatty liver of the first stage to the sparsely infiltrated liver of the third stage. We have not been discouraged by the fact that sometimes after a period of over two months we could still find in the livers of the treated group the same slightly fatty appearance (the third stage) as in livers of the control group. It

should be stressed that sometimes it is difficult to differentiate by biopsy a liver in the third stage from a liver in the fourth stage.[12] Moreover, we are satisfied with the results given by choline administration, since this substance was used in conjunction with the lipotropic basic diet, rich in proteins and low in fats, given both groups.

It is obvious that these data indicate a general and statistically valid result of choline therapy rather than universal success. The first two cases in the treated group, for example, indicate that failures are occasionally to be expected.

SUMMARY

A multiple deficiency syndrome observed among urban children in Chile is characterized by liver steatosis. The effect of choline on the liver in that syndrome was investigated by periodically repeated puncture biopsies in two groups of infants, both receiving a high protein, low fat diet. Twenty-three of these infants received a daily dose of 5 Gm. of choline hydrochloride during a minimum period of 10 days. Eighteen received no choline.

It is shown that in the first group the removal of fat from the liver was accelerated, as shown by the greater number of patients reaching stages of less fatty infiltration in a given length of time.

Our results are a direct proof of the lipotropic action of choline on the human liver, at least in patients with this form of liver disease.

Dr. Clement A. Smith, of Harvard University, gave advice during the preparation of the manuscript.

DYSENTERY DUE TO SULFONAMIDE-RESISTANT SHIGELLA SONNEI CONTROLLED WITH CHLOROMYCETIN®

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CINCINNATI

OVER a period of 10 days five of 28 children in one unit of the Children's Hospital became acutely ill with fever and severe diarrhea. This unit consisted of six small wards, of four and five cubicles each. These five children had been admitted to the hospital 8, 8, 9, 30 and 135 days previously because of some other condition not referable to the gastrointestinal tract. The five patients were in four wards of four cubicles each. Two patients were in the first and third cubicles in one ward; the three other patients were in three separate wards. According to the order in which intestinal symptoms developed in these patients, they had been in the hospital 30, 8, 135, 8 and 9 days.

Cultures taken of stools at the onset of symptoms were positive for Shigella sonnei. Each patient was isolated as soon as the result of the stool cultures was known, and sulfadiazine, 1 to 1½ grains (0.6 to 0.9 Gm.) for each pound (0.5 Kg.) of body weight per 24 hours, was given as therapy. The exception was one patient with a nephrotic syndrome of glomerulonephritis, whose initial therapy was with chloramphenicol (chloromycetin®), 250 mg. every eight hours, changed on the third day to 250 mg. every four hours. Oral medication was resisted by this patient, and after seven days the chloramphenicol was given rectally, 125 mg. every four hours. Subsequent cultures of this patient's stools were negative for S. sonnei after two days of therapy. In contrast, repeat cultures of the stools of the four patients treated with sulfadiazine remained positive for S. sonnei.

The acute phase of the infection in all patients averaged 1½ days of fever and seven days of diarrhea (charts 1 to 5). In one patient (chart 3) a recurrence of fever and liquid stools developed after sulfadiazine administration had been discontinued for three days. When sulfadiazine therapy was reinstituted, the fever subsided.

From the Children's Hospital Research Foundation and the Department of Pediatrics of the University of Cincinnati College of Medicine.

At this stage we became concerned with two possibilities, first, that the strains of S. sonnei might be resistant to sulfonamides and second, that there might be a carrier among the personnel who was responsible for the sporadic development of the rather widely separated cases.

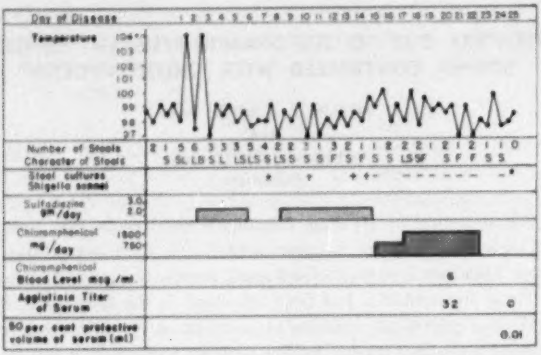

Chart 1.—Laboratory data on patient J. P. with S. sonnei dysentery, age 1.5 years, weight 17,236 Gm. (38 pounds). *S* indicates soft; *L*, liquid; *B*, blood, and *F*, formed. * S. sonnei was not isolated from four subsequent stool cultures.

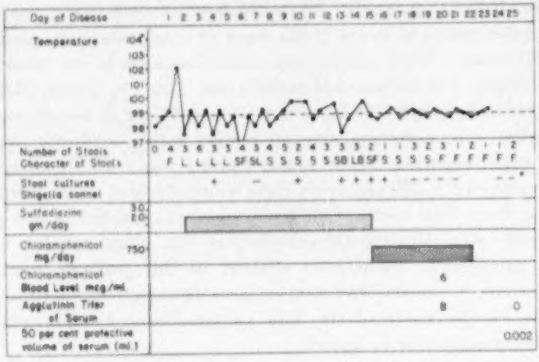

Chart 2.—Laboratory data on patient B. B. with S. sonnei dysentery, age 2.3 years, weight 11.2 Kg. (24 pounds, 10 ounces). *S* indicates soft; *L*, liquid; *B*, blood, and *F*, formed. * S. sonnei was not isolated from four subsequent stool cultures.

Accordingly, studies were instituted to obtain information regarding both possibilities. Data were obtained first on the second possibility. Stool cultures were obtained on all personnel having any contact with the patients. These cultures revealed within 18 hours the presence of S.

sonnei in the stool from a nurses' aide who was apparently healthy. Three months previously, she had been off duty for three days with a mild diarrhea, had not received any therapy and had been free from symptoms since. She was hospitalized and isolated, and treatment was

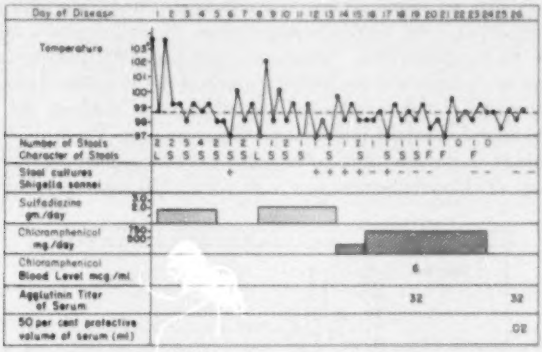

Chart 3.—Laboratory data on patient B. R. with S. sonnei dysentery, age 1 year, weight 12,474 Gm. (47½ pounds). *S* indicates soft; *L*, liquid, and *F*, formed.

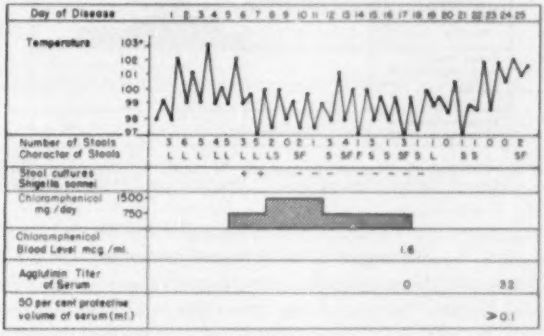

Chart 4.—Laboratory data on patient J. N. with S. sonnei dysentery and complicating nephritic syndrome of glomerulonephritis, age 3 years, weight 15.4 Kg. (34 pounds). *S* indicates soft; *L*, liquid, and *F*, formed.

started with sulfadiazine, 1 Gm. every four hours. In our past experience with use of sulfonamide therapy [1] for Shigella infections, we had usually

1. Cooper, M. L.; Zucker, R. L., and Wagoner, S.: Sulfathiazole for Acute Diarrhea and Dysentery of Infants and Children, J. A. M. A. **117**:1520-1523 (Nov. 1) 1941.

observed not only rapid clinical improvement but also early disappearance of viable shigellas from the stools. The persistence of stool cultures positive for S. sonnei made it seem likely, therefore, that we might be dealing in these patients with sulfadiazine-resistant strains. In vitro sensitivity studies, using two sulfonamides and four antibiotics (table 1), did show that the initial strains of S. sonnei isolated from each patient and the carrier were markedly resistant to the sulfonamides and susceptible to the antibiotics. Sulfadiazine sodium, 2,500 micrograms per milliliter of medium, did not inhibit growth of the shigellas. In contrast, 3 micrograms of chloramphenicol per milliliter of medium did inhibit growth, as did also 6.25 micrograms of aureomycin. These findings led to a change in therapy from sulfadiazine to chloramphenicol. The range of dosage of chloramphenicol was from 125 to 250 mg. every four hours

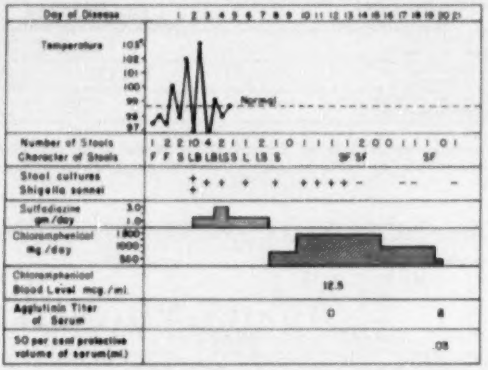

Chart 5.—Laboratory data on patient K. M. with S. sonnei dysentery, age 1.5 years, weight 11,340 Gm. (25 pounds). *S* indicates soft; *L*, liquid, and *F*, formed.

to 250 mg. three times a day. When chloramphenicol therapy was begun, stool cultures became negative for S. sonnei within an average of four days. However, chloramphenicol administration was continued for an average of 10 days, the range being from eight to 12 days. There was no evidence of toxicity, and we were impressed with the rapidity with which chloramphenicol controlled the situation and eliminated shigellas from the intestinal contents. In contrast, before the start of chloramphenicol therapy, stool cultures of the four patients being treated with sulfadiazine had continued to show the presence of S. sonnei for an average of 12 days. After chloramphenicol administration was discontinued an average of four stool cultures negative for S. sonnei were obtained on each subject in the follow-up bacteriologic study. In the case of the carrier, follow-up stool cultures were obtained over a period of 23 days. At this writing we

have not found any reference to the use of chloramphenicol in treatment of bacillary dysentery.[1a]

Chloramphenicol levels in the serum from the patients and carrier were 1.6, 6, 6, 6, 12.5 and 25 micrograms per milliliter. The highest level, 25 micrograms per milliliter, occurred in the adult carrier, 21 years of age, who was receiving a total of 2 Gm. of chloramphenicol a day (chart 6). The next highest blood level, 12.5 micrograms per milliliter, was found in the serum of patient K. M., aged 1½ years and weighing 25 pounds (11,340 Gm.), who was receiving 1.5 Gm. a day (chart 5). Three patients had blood levels of 6 micrograms per milliliter. Two of these patients were receiving 0.75 Gm. a day (charts 2 and 3), and the third patient, 1.5 Gm. a day (chart 1). The lowest blood level, 1.6 micrograms per milliliter, was found in the serum of patient J. N., aged

TABLE 1.—*In Vitro Sensitivity Tests of Strains of S. Sonnei Isolated from the Stools of Five Patients and One Carrier*

		Micrograms per Milliliter					
Patient	Inoculum, Number of Bacteria	Sulfadiazine Sodium	Sulfapyrazine Sodium	Chloramphenicol	Aureomycin Hydrochloride	Dihydrostreptomycin Sulfate	Penicillin G Sodium
J. P.	95	>2,500	>5,000	3.13	6.25	7.8	18.78
B. B.	53	>2,500	>5,000	3.13	6.25	7.8	18.78
B. R.	70	>2,500	>5,000	3.13	6.25	7.8	18.78
J. N.	58	>2,500	>5,000	3.13	6.25	7.8	18.78
K. M.	72	>2,500	>5,000	3.13	3.13	7.8	18.78
Y. L.*	108	>2,500	>5,000	3.13	6.25	7.8	18.78

* This patient was the carrier, a nurses' aide, on the same floor with the patients.

3 years, who had nephrosis and whose medication had been changed from oral to rectal (chart 4).

These blood levels were similar to those reported by others using chloramphenicol. Ley, Smadel and Crocker[2] administered chloramphenicol to two normal young adults for the purpose of evaluating their blood levels. An initial dose of 2 Gm. gave blood levels at the end of two hours slightly over 20 and 30 micrograms per milliliter of serum. A single dose of 1 Gm. gave at the end of two hours blood levels of 5 and 15 micrograms per milliliter of serum. Two hundred milligrams every two hours did not give detectable levels. Woodward, Smadel and

1a. Since this paper was submitted for publication, an article has appeared by Ross, S. and others (Chloramphenicol [Chloromycetin®] Therapy in Shigella Enteritis, J. A. M. A. **143**:1459 [Aug. 26] 1950). In this article the authors refer to an earlier publication (Ross, S. and others: Treatment of Shigella Enteritis with Oral Streptomycin, J. A. M. A. **141**:183 [Sept. 17] 1949) which we had not seen.

2. Ley, H. L.; Smadel, J. E., and Crocker, T. T.: Administration of Chloromycetin to Normal Human Subjects, Proc. Soc. Exper. Biol. & Med. **68**:9-12, 1948.

Ley,[3] during their treatment of typhoid patients with chloramphenicol, obtained blood levels of 45 micrograms per milliliter with doses of 4 Gm. a day; 40 micrograms per milliliter with doses of 3.5 Gm. a day; 20 micrograms per milliliter with doses of 2 Gm. a day, and less than 10 micrograms per milliliter with doses of 1 Gm. a day.

Blood serum agglutinin titers were determined on two serum samples from each patient tested with his own strain of Shigella. The serum samples were obtained at an interval of one week during the third or fourth week following onset of symptoms. The highest titer for two patients was 8, and for the other four subjects it was 32. In two patients the titers increased; in two the titers decreased, and in the other two patients the titers did not change. These titers (charts 1 to 6) were better than those reported by us[4] in a study of serologic antibody

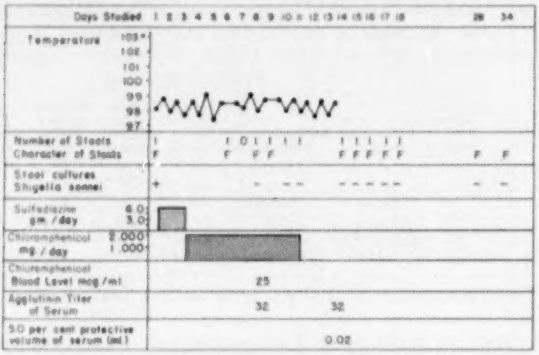

Chart 6.—Laboratory data on patient Y. L., a nurses' aide, the carrier of S. sonnei dysentery, age 21 years, weight 52.1 Kg. (115 pounds). *F* indicates formed.

responses in children of a similar age group convalescing from bacillary dysentery. It would appear that chloramphenicol had not suppressed the production of specific agglutinins.

EXPERIMENTAL OBSERVATIONS

For the in vitro sensitivity tests, cultures were maintained in the refrigerator in semisolid medium prepared from brain-heart infusion (Difco) plus 0.2 per cent nutrient agar (Difco). In preparation for the sensitivity tests, 0.5 ml.

3. Woodward, T. E.; Smadel, J. E., and Ley, H. L.: Chloramphenicol and Other Antibiotics in the Treatment of Typhoid Fever and Typhoid Carriers, J. Clin. Investigation **29**:87-99, 1950.

4. Cooper, M. L., and Keller, H. M.: Studies in Dysentery Vaccination: II. Humoral Antibody Content of Sera from Children Convalescent from Dysentery. J. Immunol. **58**:357-360, 1948.

of semisolid culture was inoculated into 9 ml. of brain-heart infusion. This culture was incubated two hours and then diluted to equal in turbidity a standard suspension containing 50,000,000 bacteria per milliliter. Twofold dilutions of two sulfonamides and four antibiotics were made in brain-heart infusion. One milliliter of each drug dilution was inoculated with 0.1 ml. of a 1:100,000 dilution of the standardized culture. The resultant drug dilution cultures were incubated 20 hours at 37 C., after which a reading was made of the least amount of each drug which inhibited growth.

The data in table 1 show that 2,500 micrograms of sulfadiazine sodium per milliliter of medium and 5,000 micrograms of sulfapyrazine sodium [5] per milliliter of medium did not inhibit growth. In contrast, 3.13 micrograms of chloramphenicol [5] per milliliter inhibited growth of all six strains of S. sonnei. Aureomycin hydrochloride,[5] 6.25 micrograms per milliliter, inhibited growth of five strains and 3.13 micrograms per milliliter inhibited growth of one strain. Dihydrostreptomycin sulfate, 7.8 micrograms per milliliter, and penicillin G sodium, 18.78 micrograms per milliliter, inhibited growth of all six strains.

Alexander, Leidy and Redman [6] reported inhibition of growth of shigellas by 3 to 10 micrograms of chloramphenicol per milliliter of medium, 3 to 5 micrograms of aureomycin per milliliter and 25 micrograms of streptomycin per milliliter. McLean, Schwab, Hillegas and Schlingman [7] reported inhibition of growth of S. sonnei by 2.5 to 5.0 micrograms of chloramphenicol per milliliter. Smith, Joslyn, Gruhzit, McLean, Penner and Ehrlich [8] found 0.2 and 0.33 micrograms of chloramphenicol to have a bacteriostatic action on S. sonnei.

Chloramphenicol blood levels were determined by the following method. Twofold dilutions of the blood serums were prepared in sterile brain-heart infusion (Difco). Twofold dilutions of sterile chloramphenicol were also prepared in brain-heart infusion, over a range of 50 to 0.195 micrograms per milliliter. A standard culture of the test organism (Shigella sonnei, Parke, Davis 04628)[9] was prepared by inoculating 0.5 ml. of semisolid culture into 9 ml. of brain-heart infusion, incubating the culture for two hours and then standardizing it to equal in turbidity a standard suspension containing 50,000,000 bacteria per milliliter. To 0.5 ml.

5. The sulfapyrazine sodium was supplied by Mead Johnson & Company, Evansville, Ind.; the chloromycetin, by Dr. E. A. Sharp, of Parke, Davis & Company, Detroit, and the aureomycin hydrochloride, by Dr. Stanton M. Hardy, of Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

6. Alexander, H. E.; Leidy, G., and Redman, W.: Comparison of the Action of Streptomycin, Polymyxin B, Aureomycin and Chloromycetin on H. Pertussis, H. Parapertussis, H. Influenzae and 5 Enteric Strains of Gram-Negative Bacilli, J. Clin. Investigation **28**:867-870, 1949.

7. McLean, I. W.; Schwab, J. L.; Hillegas, A. B., and Schlingman, A. S.: Susceptibility of Micro-Organisms to Chloramphenicol (Chloromycetin), J. Clin. Investigation **28**:953-963, 1949.

8. Smith, R. M.; Josyln, D. A.; Gruhzit, O. M.; McLean, I. W.; Penner, M. A., and Ehrlich, J.: Chloromycetin: Biologic Studies, J. Bact. **55**:425-448, 1948.

9. The strain of S. sonnei used was supplied by Dr. E. A. Sharp, of Parke, Davis & Company.

of each dilution of serum and to 0.5 ml. of each dilution of chloramphenicol was added 1.5 ml. of 1:10,000,000 dilution of the standardized test culture. After an incubation period of 20 hours at 37 C., a record was made of the highest dilution of serum and the least amount of chloramphenicol in which growth was not visible. The serum content of chloramphenicol per milliliter was then calculated.

Agglutinin titers were determined by using a standardized suspension [10] of the Shigella from each subject and fourfold dilutions of serum from the same subject. Incubation was carried on in the water bath at 55 C. for five hours. The tubes then remained at room temperature for 17 hours before the agglutination was read. The highest dilutions showing agglutination were considered to be the titers.

The passive mouse-protective power of serum from each patient and the carrier was determined on blood serum obtained three days after the discontinuation of chloramphenicol administration. The method used in studying these serums for their content of mouse-protective antibodies was the "constant organisms passive mouse-protective test" as described in a previous publication [11] with

TABLE 2.—*Therapeutic Indexes and Results of in Vivo Sensitivity Tests in White Mice Experimentally Infected with a Sulfonamide-Resistant Strain of S. Sonnei from Patient J. P.*

	In Vivo Homologous S. Sonnei in 3 per Cent Mucin											In Vitro
	Number of L. D.$_{50}$ Doses											
Therapy, 1 Mg. by Gavage 2 Hr. After Infection	112T	28T	7.0T	1,741	435.2	108.8	27.2	6.8	1.7	0.42	0.10	Therapeutic Index*
	Number of Viable Bacteria											
	10.4M	2.6M	640T	160T	40T	10T	2,495	624	156	39	10	
None	...	...	...	5/5	5/5	5/5	4/5	4/5	4/5	1/5	1/5	
Chloramphenicol	0/5†	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	...	>110,000
Sulfadiazine	5/5	5/5	5/5	5/5	4/5	5/5	5/5	4/5	2/5	1/5	...	2.6
Sulfapyrazine	5/5	5/5	5/5	5/5	5/5	5/5	5/5	2/5	3/5	0/5	...	4.7

Inoculum, 95 Bacteria
Mcgm./Ml.
3.13
>2,500
>5,000

* Therapeutic index = $\frac{\text{L. D.}_{50}\text{ dilution for treated mice}}{\text{L. D.}_{50}\text{ dilution for untreated mice}}$ = number of L. D.$_{50}$ doses.

† The numerator is the number of mice dying; the denominator is the number of mice inoculated.

the difference that preinfection serum was not available. The L.D.$_{50}$ mouse-protective volumes of these serums were 0.002, 0.01, 0.02, 0.02, and 0.03 ml. and more than 0.1 ml. These protective volumes are similar to those observed by us previously [4] in a similar age group in which we found a wide range in the 50 per cent protective volumes. Apparently chloramphenicol had not suppressed the production of this type of humoral antibody.

Therapeutic tests—in reality, in vivo sensitivity tests—were conducted in groups of female white mice, weighing 15 to 18 Gm., infected with strains of sulfonamide-resistant S. sonnei from patients J. P. and K. M. (tables 2 and 3). Groups of mice were first infected by the intra-abdominal route with increasing numbers of median lethal doses of the Shigella suspended in sterile 3 per cent mucin. Some of these infected mice were left untreated, as controls on the virulence of the culture. Two hours after infection each of the remaining mice

10. Cooper, M. L.; Tepper, J., and Keller, H. M.: Studies in Dysentery Vaccination: IV. Primary Vaccination of Children with Monovalent Vaccines of Shigella, J. Immunol. **60**:189-203, 1948.

11. Cooper, M. L., and Keller, H. M.: Studies in Dysentery Vaccination: I. The Passive Mouse Protection Test, J. Immunol. **58**:349-356, 1948.

was given, by gavage, 1 mg. of one of the three drugs tested, chloramphenicol, sulfadiazine sodium and sulfapyrazine sodium. Sulfapyrazine sodium was used because we had found [12] that S. sonnei and S. flexneri in which resistance had been induced in vitro to sulfathiazole sodium were not resistant to sulfapyrazine sodium.

It is observed in tables 2 and 3 that chloramphenicol gave excellent therapeutic results, while sulfadiazine and sulfapyrazine gave very poor results. Chloramphenicol afforded recovery of all mice infected with all inoculums including more than 110,000 median lethal doses of Shigella from patient J. P. Chloramphenicol afforded recovery of all but one of the mice infected with all inoculums including more than 260,000 median lethal doses of Shigella from patient K. M. In contrast, almost all mice which were treated with the two sulfonamides died. These in vivo results in white mice substantiate the data obtained from the in vitro

TABLE 3.—*Therapeutic Indexes and Results of in Vivo Sensitivity Tests in White Mice Experimentally Infected with a Sulfonamide-Resistant Strain of S. Sonnei from Patient K. M.*

Therapy, 1 Mg. by Gavage 2 Hr. After Infection	In Vivo: Homologous S. Sonnei in 3 per Cent Mucin; Number of L. D.$_{50}$ Doses: 550T	64T	16T	4	1	0.25	Number of Viable Bacteria: 4,000	1,024	256	64	16	4	1	0.25	Therapeutic Index[a]	In Vitro: Inoculum, 72 Bacteria
	8.0M	2.2M	550T	138T	34T	8.5T	2T	581	133	33	8					Megm./Ml.
None	...	...	...	5/5	5/5	5/5	5/5	5/5	4/5	2/5	1/5					
Chloramphenicol	1/5[b]	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5				>500,000	3.12
Sulfadiazine	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5	...				1.3	>2,500
Sulfapyrazine	5/5	4/5	4/5	5/5	5/5	5/5	5/5	5/5	2/5	1/5	...				4.0	>5,000

[a] Therapeutic Index = $\frac{\text{L. D.}_{50}\text{ dilution for treated mice}}{\text{L. D.}_{50}\text{ dilution for untreated mice}}$ = number of L. D.$_{50}$ doses.

[b] The numerator is the number of mice dying; the denominator is the number inoculated.

sensitivity tests, in which these strains of Shigella were found to be susceptible to chloramphenicol and resistant to sulfadiazine and sulfapyrazine.

SUMMARY

Dysentery due to S. sonnei developed in five patients in one unit of the Children's Hospital over a period of 10 days.

These children had been in the hospital from eight to 135 days previous to onset of symptoms of dysentery.

Sulfadiazine therapy was instituted shortly after the onset of symptoms. Fever subsided in an average of 1.5 days; diarrhea continued for an average of seven days, and stool cultures positive for S. sonnei had persisted an average of 12 days before therapy was changed.

A nurses' aide, working in the same unit, was found to be a carrier of S. sonnei.

12. Cooper, M. L., and Keller, H. M.: Sulfonamide Resistant Shigella Paradysenteriae and Shigella Sonnei, Proc. Soc. Exper. Biol. & Med. **52**:92-95, 1943.

In vitro sensitivity tests revealed each strain of S. sonnei from the patients and carrier to be highly resistant to sulfadiazine but quite susceptible to chloramphenicol and three other antibiotics.

Therapy was changed from sulfadiazine to chloramphenicol, and all stool cultures became negative for S. sonnei within an average of four days.

The range of chloramphenicol blood levels was from 1.6 to 25 micrograms per milliliter of blood serum.

The range of blood serum agglutinin titers was from 0 to 32.

Passive mouse-protective tests with serum from the patients and carrier showed a range of 50 per cent mouse-protective volumes from 0.002 to more than 0.1 ml. of serum.

Therapeutic tests—in reality, in vivo sensitivity tests—in white mice infected with two strains of these sulfadiazine-resistant S. sonnei showed that chloramphenicol afforded recovery of all but one mouse, whereas, in contrast, sulfadiazine permitted almost all mice to die.

EFFECT OF THE NATIONAL HEALTH SERVICE OF GREAT BRITAIN ON CHILD CARE IN ENGLAND, SCOTLAND AND WALES

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THE NATIONAL Health Service is a plan to provide complete medical care for the entire population of Great Britain. It includes preventive medicine, family medicine, dental and nursing services, hospitalization, medicines and drugs and all appliances and equipment necessary for the complete care of everyone.

The Minister of Health has "the duty to promote the establishment in England and Wales of a comprehensive health service" [1] and is in supreme control. Under him is a Central Service Council of 41 members that serves in an advisory capacity. Serving the Central Council and advising it and the Minister are committees of specialists on various medical services. There is a Medical Distributing Committee which allots to the local committees the compensations for general practitioners, including traveling expenses. There is also the Medical Practice Committee which, with the local Executive Council and Medical Committee, decides where physicians should locate, and whether or not physicians shall be permitted to enter areas which are designated as oversupplied with physicians.

This comprises the central mechanism for the administration of the Act. The peripheral mechanism is administered by organizations which will be discussed below.

EXECUTIVE COUNCIL

The country is divided into 138 areas called Executive Councils. Each is administered by a committee of 24 members comprising physicians, dentists and pharmacists (fig. 1). Every general practitioner in the area who has signed to come under the National Health Service Act (18,636 of 21,000 general practitioners) is under the jurisdiction of the local council.

Pediatric Member of the American Medical Association Committee to Study the Effect of the National Health Service on Medical Practice in Great Britain.

1. National Health Service Act, 1946, chap. 81, pt. 1, sect. 1.

GENERAL PRACTITIONERS

It is the duty of the general practitioner to "provide general medical services" [2] for all persons in the area who have signed on his list. He is not expected to render services requiring skill or knowledge that he is not reasonably expected to possess. He may refer any of his patients to a specialist in any of the various branches of medicine or surgery—to an ophthalmic group for glasses or to a dentist for treatment or denture and

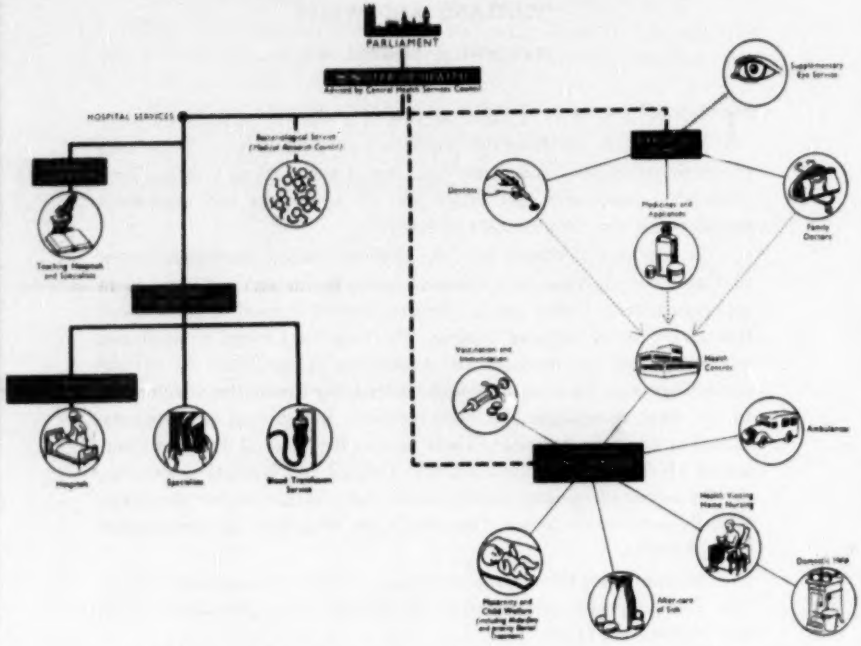

Fig. 1.—Organization of the National Health Service. The heavy solid line indicates direct responsibility; the broken heavy line, general supervisory powers; the light solid line, responsibility of Executive Councils or County and County Borough Councils; the dotted line, physicians and dentists at health centers provided by local authorities and medicines and appliances supplied at these centers, and the crossed line, temporary responsibility—eye services will ultimately be provided by Regional Hospital Boards.

he may make requests for special foods required. The general practitioner can also give free prescriptions for medicines and drugs, and all appliances that he feels the patient should have, including bandages, brushes,

2. National Health Service Act, 1946, chap. 81, pt. 4, sect. 34, paragraph 1.

cotton, orthopedic stockings and braces, splints, ice bags, vaporizers and even the much publicized wigs.

The general practitioner is paid on a capitation basis. This is presumed to be 18 s. a listed patient a year, but owing to certain deductions it is decreased to between 17 s. and 17 s. 6 d., depending on the area. The average number of patients on the list of a general practitioner is 2,000. The maximum number allowed is 4,000. This may be increased 2,400 for each assistant employed.

Other sources of compensation are a mileage fund, £150 a year for training an assistant and 5 to 7 guineas for each maternity case. The general practitioner may also serve for compensation on various government boards and institutions and charge fees for private patients whose names are not on his list.

OTHER SERVICES

A dentist is paid on a fee for service basis. These fees are reduced 50 per cent if the dentist has a gross income in excess of £4,800 a year. He may perform simple fillings and emergency treatments and minor denture repairs without permission from the Dental Board; requests for additional work must be submitted to the Dental Board.

Pharmaceutical work has increased enormously, as the government is required to "supply proper and sufficient drugs and medicines and prescribed appliances."[3] This has resulted in an almost complete disappearance of "counter sales" of these items, since they are now furnished free by prescription. However, private patients must pay full fees for all medicines and supplies, even though the Act was assumed to cover all persons.

REGIONAL HOSPITAL BOARDS

There are 14 Regional Hospital Boards which administer 3,426 hospitals, clinics and convalescent homes in England and Wales. This comprises all the hospitals except 147 teaching hospitals under 36 Boards of Governors, which are responsible to the Minister directly through their boards, and 205 clinics and hospitals that are religious institutions (fig. 2). In Scotland there are five Regional Hospital Boards, and the teaching hospitals are placed under the Regional Boards. Regional Boards are appointed by the Minister "for such areas as he may by order determine, for the purpose of exercising functions with respect to the administration of hospital and specialist services in those areas."[4]

The government has assumed all debts, payrolls and responsibilities for upkeep of the hospitals but has taken over all the endowments of

3. National Health Service Act, 1946, chap. 81, pt. 4, sect. 38, paragraph 1.

4. National Health Service Act, 1946, chap. 81, pt. 11, sect. 11, paragraph 1.

these institutions except the teaching hospitals. The endowments taken over by the government have been placed in a Hospital Endowment Fund, under the jurisdiction of the Minister.

An intern serves for one year and receives from £350 to £450 a year, less £100 a year for maintenance. If further training toward specialization is desired, the intern becomes a registrar and serves up to seven years in various grades of responsibility. The compensation begins at £670 a year and increases to £1,300. At the end of this time he may qualify as a consultant.

CONSULTANTS

The various hospitals are staffed by consultants. These physicians are examined by an Advisory Appointments Committee and appointed solely by the Regional Board.

The full time salary scale begins at £1,700 a year and is increased by £125 a year to £2,750. Part time consultants are paid on a scale of eleven half day sessions a week. In addition to this, part time consultants are paid up to 800 guineas each maximum yearly remuneration for domiciliary calls (consulting house calls). The government has also indicated that 34 per cent of the consultants are entitled to additional compensation of from £500 to £2,500 a year each, depending on their age and experience. A committee is at the present time determining the qualifications for this group.

LOCAL HEALTH AUTHORITIES

There are 83 towns and 62 counties that have certain powers and privileges which have been given and can be taken away only by an Act of Parliament. These localities carry on the following program: (1) health centers, (2) maternity and child welfare, (3) domiciliary midwifery (home delivery by a midwife who is a graduate nurse), (4) health visiting, (5) home nursing, (6) vaccination and immunizations, (7) ambulance services, (8) domestic help service, (9) day nurseries and (10) mental guardianship, tuberculosis (preventive and after-care) and venereal disease services.

Inasmuch as the greater part of the prophylactic health service given to English children is rendered by local authorities, this will be enumerated in more detail than above. For the infant, home instruction and nursing service are rendered to the mother immediately after the birth of the baby, if at home, or when she returns home from the hospital (the minimum postpartum hospital stay is 10 days). If there are other small children or any household difficulties, domestic help is furnished up to 14 days. When the mother can take the baby to an Infant Welfare station, medical examination and feeding instruction are given through

the second year of life. These stations are conducted two or three times a week at easily accessible locations.

Vaccination for smallpox is not compulsory but is encouraged for children from 4 months to the end of the first year. Diphtheria immunization is urged and usually given to children from 8 to 12 months of age, with a reenforcing dose at 5 years and another at 10 years. These immu-

Fig. 2.—Regional hospital areas. Fourteen Regional Hospital Boards are responsible for the administration of the hospital and specialist services in England and Wales (with the exception of the 36 teaching hospitals, each of which has its own board of governors). Regional Hospital Administration boundaries are indicated by heavy lines, Regional Head Offices by black dots and county boundaries by dotted lines.

nizations are given at the stations by the local authorities' doctors. Recently the government has authorized a payment of 5 s. 5 d. to each general practitioner if immunization is given by him. Whether general practitioners will give the majority of these immunizations in the future

remains to be seen. Vitamin D is given at 1 month of age. This is furnished gratis by the government. Vitamin C is given at 1 month of age and furnished for 5 d. and a food stamp for a month's supply. This is to discourage its use by the entire family.

Preschool children are seen at the Infant Welfare Station three to four times a year, and appropriate instructions and treatment are given as needed. The classes in orthopedic exercises are of particular interest. These are given to all children suffering from flat feet, faulty posture and various limb defects. Nursery schools are also furnished for the children of working mothers. The children stay there from 8 a. m. to 6 p. m. and receive various exercises, rest and instructions. They are also given three meals a day which are furnished at no cost to the mothers.

The School Health Service consists of periodic examinations by a school nurse and vision and audiometric tests. Medical examinations are given as soon as possible after the child's entry into the school, somewhere between the ages of 5 and 6 years. They are also given at 7 to 8 years and 10 to 11 years and during the last school year. They are also given at the request of the parents, teachers or the divisional officer. The treatment of defects is being gradually absorbed into the hospital service. Each child has a family physician, and the Regional Hospital Board is responsible for hospital and special treatment. Special school clinics (vision, hearing and rheumatic fever) are gradually being absorbed into the hospital service. The Regional Hospital Board now pays the specialist in charge of each clinic. Dental treatment for school pupils remains the function of local educational authorities.

Nutrition clinics and clinics for minor ailments are still operated by the local health authorities. In London 400 beds are kept at Queen Mary's Hospital for children with rheumatism. On discharge the patients usually remain under observation at one of the rheumatism-supervising centers. Special education is provided for the blind, deaf, epileptic, diabetic, crippled and subnormal groups.

The local health authorities are also responsible for the control of communicable diseases in the schools, for child guidance clinics, speech therapy and the follow-up and medical supervision of all schools. They are responsible for the care of all homeless and delinquent children. There is also a large nursing staff that administers the treatment centers, attends the medical inspectors and provides the nurses for special schools and residential establishments.

PEDIATRIC PRACTICE

Pediatric practice in England is quite different from that in the United States. Prophylactic public health measures and general care of practically all children are the responsibility of either the local health authorities or the general practitioner. According to the National Health

Act, every child in the United Kingdom has his own physician and is registered on the list of the general practitioner chosen by his parents. Theoretically the child is entitled to a medical examination at the physician's office any time the parents so desire or to a home visit if sick. Actually most mothers prefer to take their babies to Infant Welfare stations operated by the local health authorities. One mother of the middle class informed me that her 18 month old child had never been to a physician's office but had always been examined at the local Infant Welfare station.

The reason for this is that many mothers prefer waiting with other mothers and children at a welfare clinic rather than having a much longer wait in their physician's waiting room with sick people. When it is realized that many general practitioners will average 60 patients for a two hour office period, it will be understood why this wait is not agreeable to the average mother with a fussy baby. Since the adoption of the Act, the overloading of all general practitioners' office hours by patients with all sorts of unnecessary requests and complaints has been observed in all areas. Not only must the mother wait her turn with the child for a period of one to two hours in an atmosphere not congenial and perhaps even injurious to the child's health, but the very short consulting time that must be given each individual when the physician is finally reached makes such care inferior to the care of the welfare clinic.

If the child is found to be sick at one of the welfare clinics or by his own physician, appropriate treatment is given within the physician's time and ability. If further pediatric advice is desired, the child is referred to the outpatient department of a hospital if the child is ambulatory. If the child is sick at home, the physician has the right to ask for a house visit by a pediatric consultant. If hospitalization is necessary, it can be obtained only through the pediatric consultant.

In England, Wales and Scotland the pediatrician is the hospital full or part time consultant. He has arrived at consultant status by six to eight years of hospital pediatric specialization and was appointed to the hospital through the Regional Board. He practices usually part time at the hospital, working certain periods in the outpatient department and seeing patients referred by the general practitioners. He usually also has one of the pediatric services at his attending hospital and conducts various special clinics. In his remaining time he makes home calls in consultation with the general practitioners of his area and conducts his small private practice, if any. No child can be admitted to a hospital without seeing the pediatric consultant either in the outpatient department or after a home consultation.

Pediatricians were relatively new as specialists before World War II and have increased in number and authority since the war. It must be

emphasized that at the present time the bulk of pediatric care is in the hands of the local authorities and the general practitioner. However, many pediatric specialists will conduct some of the Infant Welfare clinics for the local authorities and do other pediatric work. Inasmuch as a community of 100,000 may have only one pediatric specialist, it can be easily seen that this field is far from thoroughly covered.

A word may be said here about private practice. There is almost no private practice in pediatrics among the general practitioners. Specialists will have a few children that are brought to them for paid treatment, but the factors that are driving out private practice from all medical care in Great Britain operate in pediatrics as well. The first factor is the extra expense of drugs and medicines; as mentioned before, private patients must pay the full cost of all medicines prescribed, even though they are all citizens and have paid their share in taxes toward the National Health Act. The second drawback is the inability to obtain hospital beds for paying patients and the extra cost. Only a small number of beds are set aside for paying patients, and the cost for such beds has been doubled in the last two years. As one pediatrician told me, "I do not even bother to try to get any of my private patients into a hospital on a paying basis but just put them in the usual free ward beds and relinquish their care until the completion of their hospital stay."

CHILD CARE

The curve of mortality and morbidity has been steadily decreasing since World War II, before the passage of the National Health Act, and, according to the Ministry of Health, it will be impossible to judge the effect of the Act for 10 years. However, certain generalities and trends can be noted. Unless there is a substantial drift of physicians from general practice and specialties to public health work, the prophylactic care of infants will probably not be bettered and may even deteriorate. At the present time one rarely sees a malnourished child, and rickets and scurvy have disappeared. This is partly due to a campaign of many years for breast feeding (95 per cent of the newborn infants at 10 days of age are breast fed). There is, however, a considerable amount of tuberculosis among children. In almost every hospital visited, children with tuberculosis numbered 10 to 15 per cent of the patients in the children's wards. This is almost entirely due to the shortage of beds for adults with active lesions who act as carriers. However, the shortage of beds is a holdover from the building destruction and the shortage of nurses.

It is in the treatment of childhood defects that the National Health Act has caused the greatest changes. Instead of close association with the local health authorities over hospitals all under uniform direction, proposals for any change have to be agreed to by several hospital boards and

in some cases by a number of teaching hospitals. Outpatient departments to which ambulatory children must be referred are horribly overcrowded. The daily census frequently has increased from 10 to 70 per cent. As one hospital director said, "We now have an appointment system under which the patient, instead of waiting from 8 a. m. to 6 p. m. in the waiting room as formerly, can now wait two months at home."

Overcrowding is all the result of a vicious cycle. The great overflow of patients into the general practitioner's office with minor or trivial complaints and the mass of paper work make such a load on the harried physician that he, in self protection, refers many persons to the specialists in the outpatient department. As one physician said, "We are not voluntary physicians but salaried copy clerks." Many patients also demand to be referred to specialists. This, in turn, overcrowds the outpatient departments and associated departments such as roentgenology and laboratory services. The waiting time in most outpatient departments for a barium gastrointestinal study is three weeks. This would mean that for such an examination the appointment to the specialist would take three weeks and the barium examination three weeks more or a total of six weeks.

The hospitals are filled to overflowing and have long waiting lists, but, fortunately, in most hospitals, a place can be found for acutely ill children. In London there is an Emergency Bed Service that maintains a central telephone clearing house for available beds and placement of patients at the request of local physicians. The waiting time for a tonsillectomy varies from eighteen months to two years in all hospitals visited. While this provokes the jocular observation that by the time the child can be taken for a tonsillectomy the need has disappeared, it is very distressing for the occasional child with large hypertrophic tonsils, cervical adenitis and, often, danger of a mastoid involvement. They are simply caught in the mill unless they can obtain priority.

One of the most disturbing effects of the National Health Act is the breakdown or deterioration of the prophylactic dental treatment of school children, owing to the serious loss of dental surgeon staff who have transferred their services to the National Health Service. Dentists who have been employed on a salary are reluctant to continue in the face of the opportunities for earning several times their present rate of compensation. Large numbers have left the government service, and there has been difficulty in offering any increase in salaries to medical and dental officers, because any increase for them would result in a similar increase for other employees. The introduction of the general dental service has indirectly caused irreparable damage to the teeth of hundreds of thousands of school children and may bring about in the near future the total collapse of all the priority dental services.

EFFECT ON THE PATIENTS

The basic principle of the National Health Service Act, that no person shall by lack of means be debarred from any necessary medical advice or appliance, is excellent. It is argued that before the adoption of the Act only the family wage earner was protected by medical benefits and care under the panel system and that his wife and family were uncared for, if in the low income group. This, of course, was not the case. The local health authorities conducted Infant Welfare stations, antepartum and postnatal clinics, home midwife delivery, free nursing service and house calls, all of which have been practically unchanged since the initiation of the Act.

Local government furnished municipal and county hospitals, where all care was free. Voluntary hospitals gave aid and free care to the indigent and low income groups. No one was neglected; yet there had been so much talk about free medical care that these patients accept the care now with a feeling of surprised gratitude, forgetting how completely the practically free services of voluntary hospitals were taken for granted.

As has been stated before, the functioning of the Act has actually disrupted some of the old local government services, namely dental care and treatment of defects. Many patients would actually rather go on with the old free hospital relation than trust to other medical advice. Many mothers would now rather bring their children directly to a hospital clinic than have them under the care of their own physicians to whom they should turn for advice.

Perhaps some of this attitude is due to the confusion and overlapping of the services rendered by the four major agencies. For example, a newborn infant in the home will be under the care of a midwife who is under the jurisdiction of the local health authorities. Should the infant become ill, she is expected to call in the general practitioner on whose list the infant had been placed. He is under the Local Executive Council through which he makes his reports and receives his remuneration. If the general practitioner feels that the infant is suffering from an illness for which he desires advice, he can call in a pediatric consultant for a house call, who is under the jurisdiction of the Regional Hospital Board. Now, if the child is ill enough to require hospitalization, the pediatric consultant will enter him in a regional hospital, or if the consultant is on the teaching staff of a teaching hospital he will be under the Board of Governors of the teaching hospital. This is referred to by hospital directors generally as "organized chaos."

It is, therefore, possible in a case of simple gastroenteritis of a newborn child to use the professional personnel of four different government agencies. This obviously does not help toward the personal feeling and sense of responsibility that a doctor is accustomed to feel toward his

patients. All this assumes that the infant will be admitted to the hospital at once, which may not happen. However, it is only fair to state that as a general rule infants and children are usually found beds almost immediately—quite different from the long bed wait for adults.

So much for the effect on the low economic group and the indigent. What is the effect on the upper and middle classes? It is hard for us in America to imagine this great leveling process. In any such experiment it must be remembered that if anything is raised from the bottom something must also be lowered from the top if a common level is to be obtained. This results in generalized mediocrity. This National Health Service is an essential part of a scheme for completely nationalized public health in a socialistic country. The American mother must try to visualize having her baby delivered in a maternity or general hospital with ward care or at home by a midwife (a graduate, qualified, obstetric nurse) and then taking her baby to an Infant Welfare station for its infant years and to a preschool station or nursery school for its childhood period. The medical examinations will be made in school clinics and prophylactic immunizations given by public health doctors and nurses during his school life, and if any acute illness should occur the child will receive medical attention similar to that given by the city or county health department physicians in our country today. If she can visualize this, she will have the exact picture.

It has been said that the National Health Service will increase the health of the total population and, thereby, their productivity. This increased productivity will, in turn, increase the national income and raise the standard of living for the entire country. Actually the situation is similar to that of the man who tried to lift himself by his bootstraps. The individual must eventually learn that in this life nothing is given away free without recompense in some direction. It is the individual who always pays eventually, either by direct or indirect taxation. The total budget of the English people amounts to 40 cents out of every dollar earned.

Certainly a 40 per cent levy of taxation is far from a free economy and actually places such a burden on the taxpayer that the very things he desires for a better way of life cannot be obtained. When one cannot have the right to control his own funds, the incentive to save and the will to work are destroyed. Life offers always the will to work and produce and enjoy the fruits of our labor. In a planned economy these rights are lost under the weight of central supervision and authority, and life becomes nothing but a dreary treadmill of round after round of futility.

952 North Michigan (11).

ENRICHMENT OF MILK VITAMIN A IN NORMAL LACTATING WOMEN

A Comparison Following Administration of Vitamin A in Aqueous and Oily Mediums

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THE PURPOSE of this investigation was to determine whether vitamin A in aqueous dispersion given to lactating women increases the vitamin A content of the milk secreted more effectively than vitamin A administered in oil.

Recent investigations have well established that the absorption of vitamin A from aqueous dispersions is far more efficient than when vitamin A is administered in oil. This was shown by the results of (1) vitamin A tolerance tests in newborn infants, older children and adults, (2) vitamin A storage tests in rats and (3) vitamin A balance studies.[1]

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Presented in part before the One Hundred and Fourteenth Meeting of the American Chemical Society, Division of Biologic Chemistry, Washington, D. C., Aug. 30, 1948.

1. (*a*) Sobel, A. E.; Gottfried, S. P., and Kramer, B.: A Comparison of Vitamin A Serum Levels in Children Following the Oral and Intramuscular Administration of Vitamin A in Oily and Aqueous Media, in the Abstracts of the Papers Read Before the One Hundred and Tenth Meeting of the American Chemical Society, Division of Biological Chemistry, Chicago, Sept. 11, 1946. (*b*) Kramer, B.; Sobel, A. E., and Gottfried, S. P.: Serum Levels of Vitamin A: Comparison Following the Oral and Intramuscular Administration of Vitamin A in Oily and Aqueous Medium, Am. J. Dis. Child. **73**:543 (May) 1947. (*c*) Popper, H.; Steigmann, F., and Dyniewicz, H. A.: Treatment of Endogenous Hypovitaminemia in Liver Disease, J. Lab. & Clin. Med. **32**:1403 (Nov.) 1947. (*d*) Sobel, A. E.; Sherman, M.; Lichtblau, J.; Snow, S. D., and Kramer, B.: Comparison of Vitamin A Liver Storage Following Administration of Vitamin A in Oily and Aqueous Media, J. Nutrition **35**:225 (Feb.) 1948. (*e*) Lewis, J. M.; Bodansky, O.; Birmingham, J., and Cohlan, S. Q.: Comparative Absorption, Excretion and Storage of Oily and Aqueous Preparations of Vitamin A, J. Pediat. **31**:496 (Nov.) 1947. (*f*) Sobel, A. E.; Besman, L., and Kramer, B.: Vitamin A Absorption in Newborns, Older Children, Adults and A Storage in

Most of the absorption with aqueous mediums takes place in the upper part of the jejunum, and with oily solutions, in the lower part of the jejunum.[2] In addition to improved absorption, the blood vitamin A levels obtained with aqueous mediums are far higher than those obtained with oily solutions. Theoretically, the transference of vitamin A across a membrane should be higher with higher serum levels (the rate of diffusion across a membrane, if there are no other factors involved, increases directly with the concentration of the diffusing substance). In addition, the vitamin A in aqueous dispersion may be more diffusible than in an oily solution because of the possibility that the particle size of the vitamin A–containing lipids in blood are smaller than in the usual circumstances.[3]

The relatively poor transfer of the fat-soluble vitamins to milk has been shown conclusively (and is again indicated in this paper) for both vitamin A and vitamin D.[4] This is a practical nutritional problem for infants that are breast fed. The recent recommendation prepared by the Committee on Fetus and Newborn and endorsed by the American Academy of Pediatrics states, "It is recommended that efforts be made to have every mother of a full term infant nurse him."[5] Potter has called attention to the tremendous decrease in infant mortality produced by the program of the Chicago Health Department in which breast milk

Rats, Federation Proc. **7**:373 (March) 1948. (*g*) May, C. D., and Lowe, L.: The Absorption of Orally Administered Emulsified Lipid in Normal Children and in Children with Steatorrhea, J. Clin. Investigation **27**:226 (March) 1948. (*h*) Popper, H.; Steigmann, F., and Dyniewicz, H. A.: The Influence of Anti-Oxidative and Dispersing Agents on Vitamin A Absorption: Therapeutic Implications in Endogenous Hypovitaminemia, Gastroenterology **10**:987 (June) 1948. (*i*) Popper, H.; Steigmann, F.; Dubin, A.; Dyniewicz, H. A., and Hesser, F. P.: Significance of Vitamin A Alcohol and Ester Partitioning under Normal and Pathologic Circumstances, Proc. Soc. Exper. Biol & Med. **68**:676 (Aug.) 1948. (*j*) Davidson, D. M., and Sobel, A. E.: Aqueous Vitamin A in Acne Vulgaris, J. Invest. Dermat. **12**:221 (April) 1949. (*k*) Sobel, A. E.; Rosenberg, A.; Geduldig, R.; Engel, E.; West, M., and Kramer, B.: Aqueous Dispersions of Fat-Soluble Vitamins, Federation Proc. **8**:253 (March) 1949. (*l*) Sobel, A. E.; Besman, L., and Kramer, B.: Vitamin A Absorption in the Newborn, Am. J. Dis. Child. **77**:576 (May) 1949.

2. Popper, H., and Volk, B. W.: Intestinal Absorption of Vitamin A from Aqueous and Oily Menstruum, Proc. Soc. Exper. Biol. & Med. **68**:562 (Aug.) 1948.

3. Becker, G. H.; Meyer, T., and Necheles, H.: Fat Absorption and Atherosclerosis, Science **110**:529 (Nov.) 1949.

4. Hrubetz, M. C.; Deuel, H. J., and Hanley, B. J.; Studies on Carotenoid Metabolism: The Effect of a High Vitamin A Intake on the Composition of Human Milk, J. Nutrition **29**:245 (April) 1945. Polskin, L. J.; Kramer, B., and Sobel, A. E.: Secretion of Vitamin D in Milks of Women Fed Fish Liver Oil, ibid. **30**:451 (Dec.) 1945.

5. Standards and Recommendations for Hospital Care of Newborn Infants, Full-Term and Premature, American Academy of Pediatrics, Committee on Fetus and Newborn, Evanston, Ill., 1948, p. 23.

was fed routinely to premature infants.[6] On a low vitamin A diet or when an impairment of fat absorption exists, human milk may contain an insufficient amount of vitamin A for optimum requirements. Acute vitamin A deficiency and death in some cases have been reported in breast-fed infants.[7]

In the present studies it was possible to indicate that by the administration of aqueous dispersions of vitamin A to the mother one could assure a better supply of vitamin A to the breast-fed infant.

The approach in the present study was to determine the changes in blood and milk vitamin A levels of normal lactating women starting on the fourth day after parturition. The subjects were consuming balanced diets and had received no vitamin supplementation of any kind during their stay at the hospital. Special precautions were taken that none of the subjects received liquid petrolatum or any other medicament which might interfere with the absorption of fats.

The general procedure was to take one milk and one blood specimen just prior to administration of the test dose plus additional milk specimens in the 24 hours preceding the test dose. One thousand U. S. P. units of vitamin A per pound (0.5 Kg.) of body weight was given. Blood specimens were collected from the fingertip 3, 6, 9 and 24 hours after the test dose, and milk specimens were collected 4, 8, 12, 16, 20 and 24 hours following the test dose.

To serve as a control, a similar study was made with a group not receiving any supplements.

In the first study, we compared the results obtained with a vitamin preparation previously referred to as aqueous dispersion I [8] with those obtained with a vitamin A preparation previously referred to as oil I.[9] The changes in milk vitamin A levels are given in table 1 and for serum levels in table 2. The mean values are given for milk in chart 1 and

6. Potter, E. C.: The Lessons to Be Learned from a Study of Infant Deaths, J. A. M. A. **124**:336 (Feb. 5) 1944.

7. Blackfan, K. D., and Wolbach, S. B.: Vitamin A Deficiency in Infants, J. Pediat. **3**:679 (Nov.) 1933. Thalberg, J.: Zur Casuistik der durch Inanitionzustände bedingten Hornhautgangrän, Arch. f. Augenh. **12**:315, 1883. de Haas, J. H., and Meulemans, O.: Vitamin A and Carotenoids in Blood: Deficiencies in Children Suffering from Xerophthalmia, Lancet **1**:1110 (May 14) 1938. Thatcher, H. S., and Sure, B.: Avitaminosis: Pathologic Changes in Tissues of the Albino Rat During Early Stages of Vitamin A Deficiency, Arch. Path. **13**:756 (May) 1932.

8. The preparation is called vifort. The source of vitamin A is the nonsaponifiable fraction of fish liver oil. Each 0.6 cc. contains 5,000 U. S. P. units of vitamin A, 1,200 U. S. P. units of vitamin D, 60 mg. of vitamin C, 1.8 mg. of vitamin B_1, 0.4 mg. of vitamin B_2, 3 mg. of nicotinamide, 0.3 mg. of vitamin B_6, 1.2 mg. of pantothenic acid and 16 per cent sorethytan monolaurate, which is the dispersing agent.

9. Oil I was percomorph liver oil, each gram containing 60,000 U. S. P. units of vitamin A in the form of esters and 10,000 U. S. P. units of vitamin D.

TABLE 1.—*Vitamin A Levels of Milk of Normal Lactating Women Following Administration of Vitamin A in Aqueous and in Oily Mediums*

Case No.	Preparation	Vitamin A, Micrograms/100 Cc. of Milk: Previous Test	Hours After Test Dose * 4	8	12	16	20	24	Maximum Rise
1	Aqueous dispersion I	340	340	340	440	430	390	370	100
2	Aqueous dispersion I	30	305	295	245	135	100	85	305
3	Aqueous dispersion I	290	300	445	610	440	270	...	320
4	Aqueous dispersion I	180	230	460	695	490	290	...	515
5	Aqueous dispersion I	360	280	470	445	410	380	...	110
6	Aqueous dispersion I	255	225	417	455	340	225	...	200
	Mean	229	263	421	482	371	283	228	285
7	Oil I	322	210	180	250	220	245	205	— 23
8	Oil I	198	225	302	365	250	223	365	167
9	Oil I	200	213	215	246	251	210	200	46
10	Oil I	160	135	158	182	162	141	...	22
	Mean	220	196	229	248	226	207	256	53
11	Aqueous dispersion II	211	237	300	345	320	282	276	132
12	Aqueous dispersion II	307	322	425	384	375	338	335	118
13	Aqueous dispersion II	190	104	275	290	304	160	215	200
14	Aqueous dispersion II	165	225	300	295	290	285	...	135
15	Aqueous dispersion II	157	271	420	182	140	108	...	263
16	Aqueous dispersion II	410	530	685	490	490	490	...	275
	Mean	223	282	401	331	303	277	275	187
17	Oil II	140	210	170	180	180	180	150	70
18	Oil II	170	215	135	175	170	160	...	39
19	Oil II	260	210	207	290	300	300	...	40
20	Oil II	270	248	240	250	265	276	...	6
21	Oil II	415	417	315	300	230	170	...	— 1
22	Oil II	5	9	9	11	21	...	...	15
	Mean	213	218	177	214	200	197	130	23

* The test dose was 1,000 U. S. P. units of vitamin A per pound of body weight.

TABLE 2.—*Vitamin A Levels of Blood of Normal Lactating Women Following the Administration of Vitamin A in Aqueous and in Oily Mediums*

Case No.	Preparation	Vitamin A, Micrograms/100 Cc. of Milk: Previous Test	Hours After Test Dose * 3	6	9	24	Maximum Rise
1	Aqueous dispersion I	60	360	245	120	60	300
2	Aqueous dispersion I	..	285	360	190	180	275
3	Aqueous dispersion I	25	500	...	90	40	475
4	Aqueous dispersion I	40	300	...	110	50	260
5	Aqueous dispersion I	..	...	...	...	..	...
6	Aqueous dispersion I	170	345	240	...	255	175
	Mean	74	416	348	128	115	302
7	Oil I	28	...	165	...	40	137
8	Oil I	50	400	187	...	60	350
9	Oil I	97	300	100	...	79	203
10	Oil I	25	100	48	...	31	75
	Mean	50	266	125	...	53	191
11	Aqueous dispersion II	36	317	106	97	75	281
12	Aqueous dispersion II	239	545	345	210	195	308
13	Aqueous dispersion II	25	155	180	90	45	165
14	Aqueous dispersion II	43	407	155	125	112	364
15	Aqueous dispersion II	40	222	85	51	51	182
16	Aqueous dispersion II	63	366	...	117	95	303
	Mean	79	340	176	115	94	255
17	Oil II	70	415	140	75	70	345
18	Oil II	10	30	110	50	60	100
19	Oil II	35	60	210	125	40	85
20	Oil II	55	325	60	...	60	270
21	Oil II	68	74	117	...	58	49
22	Oil II	25	30	26	78	..	53
	Mean	44	156	112	85	58	150

* The test dose was 1,000 U. S. P. units of vitamin A per pound of body weight.

for blood in chart 2. It may readily be observed that the change in milk level is distinctly higher with aqueous dispersion I than with oil I. The mean maximum rise which takes place about 12 hours after the administration of the test dose is 285 micrograms for aqueous dispersion I, and

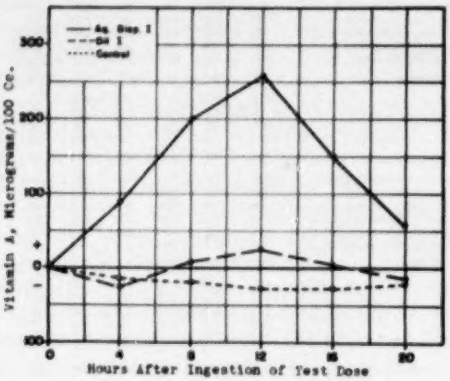

Chart 1.—Mean rises in milk vitamin A level following the administration of aqueous dispersion I and oil I to lactating women.

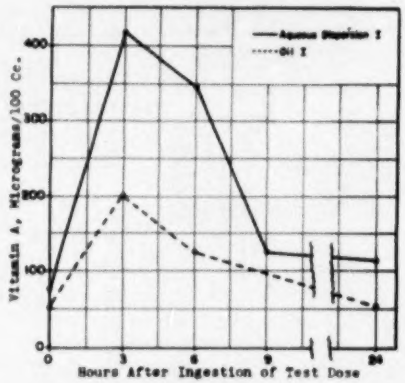

Chart 2.—Mean changes in serum vitamin A following the administration of aqueous dispersion I and oil I to lactating women.

even at the end of 20 hours the mean rise is 62 micrograms. The mean maximum rise with oil I is 53 micrograms, and at the end of 20 hours this drops to 13 micrograms below the initial level. On comparing the absorption of vitamin A from the gastrointestinal tract as measured by

the changes in vitamin A levels in the blood, one observes that there is a notable improvement in absorption with aqueous dispersion I as compared with oil I. This indicates that lactating women also absorb aqueous dispersions better than oily solutions.[10]

Since both aqueous dispersion I and oil I contain vitamins in addition to vitamin A and, moreover, the sources of vitamin A were not the same,[11] the question arose as to whether the distinctly improved absorption of vitamin A and the transfer of the latter into milk with aqueous dispersion I were due entirely to the medium employed and not to other factors present. For this reason, the preparations previously referred to as aqueous dispersion II [12] and oil II [13] were compared. In one case, the solvent was water plus dispersing agent; in the other, the solvent was corn oil. In comparing results, therefore, the only variable is the menstruum. The results are given in tables 1 and 2 and mean values in charts 3 and 4. The mean maximum rise in the milk vitamin A level which occurs about eight hours following administration of the test material was 187 micrograms and at the end of 20 hours was 54 micrograms with aqueous dispersion II. In contrast to this, the mean maximum rise in the milk vitamin A level with oil II was 23 micrograms, and at the end of 20 hours this dropped to 15 micrograms below the initial level.

It is evident again that the change in milk (chart 3) and blood (chart 4) vitamin A levels is distinctly greater with the aqueous dispersion than with the oily solution. Thus, the transfer to milk as well as absorption into blood are superior with vitamin A in aqueous dispersions as compared with vitamin A in oils. The conclusion may be drawn that the improved transfer is due to aqueous mediums.

These changes with aqueous dispersions are even more significant if one considers the fact that in the fourth to fifth day post partum when no supplements are given the milk vitamin A level actually drops, as seen in table 1 and charts 1 and 3. That milk vitamin A levels drop during the first five days post partum when no supplement is given was previously observed.[14]

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10. Footnotes 1 and 2.

11. Footnotes 8 and 9.

12. Aqueous dispersion II was the nonsaponifiable fraction of fish liver oil containing 800,000 to 1,000,000 U. S. P. units of vitamin A per gram, diluted with water containing 16 per cent sorethytan monolaurate to a concentration of 10,000 U. S. P. units of vitamin A per cubic centimeter.

13. Oil II was the same nonsaponifiable fraction diluted in corn oil to a concentration of 10,000 U. S. P. units of vitamin A per cubic centimeter.

14. Lesker, M.; Brody, J. K.; Williams, H. H., and Macy, I. G.: Human Milk Studies: Vitamin A and Carotenoid Contents of Colostrum and Mature Human Milk, Am. J. Dis. Child. **70**:182 (Sept.) 1945.

In comparing the results obtained with aqueous dispersions I and II, one can observe that the milk levels are higher with aqueous dispersion I.[15] These observations will bear further investigation.

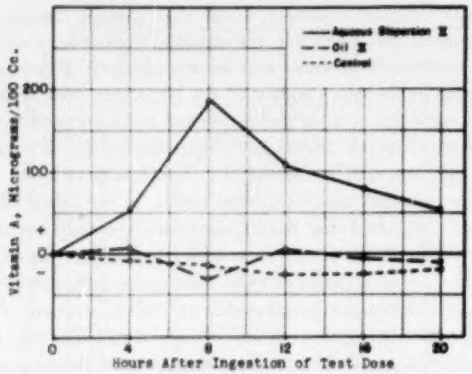

Chart 3.—Mean rises in milk vitamin A level following the administration of aqueous dispersion II and oil II to lactating women.

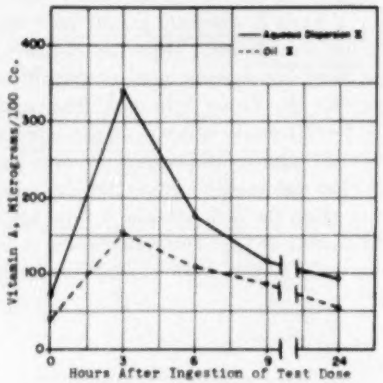

Chart 4.—Mean changes in serum vitamin A following the administration of aqueous dispersion II and oil II to lactating women.

Theoretically, at least, the degree of transfer from the blood through a membrane should be a function of the concentration of the diffusing substance. By increasing the amount of oil I administered to 3,000 U. S. P. units per pound of body weight, conditions were obtained in

15. Sobel, Sherman, Lichtblau, Snow and Kramer.[14]

which the change in blood level was the same as when 1,000 U. S. P. units per pound of body weight was administered as aqueous dispersion I. To further prove this point, by increasing the dose of oil I to 6,000

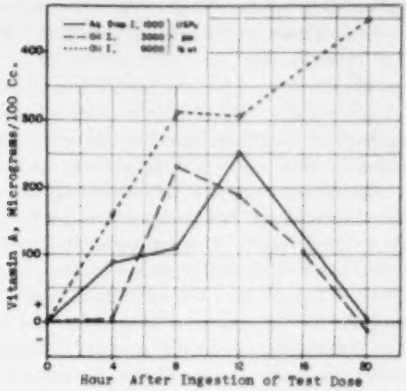

Chart 5.—Mean rises in milk vitamin A level following the administration to lactating women of aqueous dispersion I, three times as much vitamin A in oil I and six times as much vitamin A in oil I.

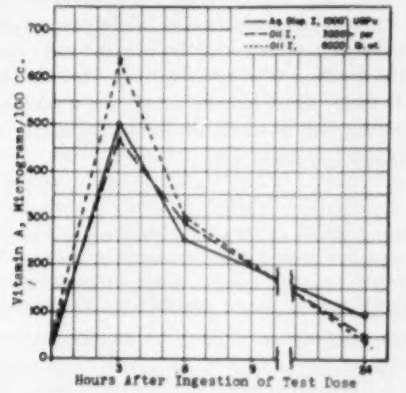

Chart 6.—Mean changes in serum vitamin A following the administration to lactating women of aqueous dispersion I, three times as much vitamin A in oil I and six times as much vitamin A in oil I.

U. S. P. units per pound of body weight, higher serum levels were obtained than with 1,000 U. S. P. units of aqueous dispersion I. The results are shown in charts 5 and 6. It is seen that with a corresponding

rise in blood levels the change in milk levels is approximately the same, the level still being somewhat higher with aqueous dispersion I. When the blood level is distinctly higher with oily solution, as was the case when six times as much oil was given, the change in milk level is correspondingly higher. The results indicate that blood concentration may be an important, although not necessarily the sole, factor in the transfer of vitamin A from blood to milk.

COMMENT

The results presented clearly indicate that the transfer of vitamin A to milk is far superior with aqueous dispersions to that obtained with oily solutions. That the superiority of the former may not simply represent a temporary increase in the first 24 hours was further confirmed by our studies with suckling rats.[15] Postpartum mother rats were placed on a vitamin A–deficient diet and fed daily one 1,500 U. S. P. unit dose of aqueous dispersion II or oil II. The suckling rats were killed on the fifth day following the administration of this supplement to the mother and the liver and kidneys examined for vitamin A.[15] (the vitamin A content of the rest of the carcass was negligible, in contrast to that of the newborn, in which more vitamin A was found in the carcass). The vitamin A storage was about four times as great in the group fed with aqueous dispersions as in the group fed with oil.

The mechanisms that regulate the composition of milk are still obscure. One of the limiting factors that can be postulated is the transport to the site of milk production of those components of milk that are not manufactured locally. Theoretically, the diffusion of a substance like vitamin A from the blood across a membrane would be proportional to the concentration gradient of the diffusing substance.

The approximate computation is

$$A = KC$$

where

A = amount of vitamin A diffusing through a unit area per unit time
C = difference in concentration of vitamin A on the two sides of a given membrane, i. e. serum vitamin A and filtrate across capillaries
K = constant depending on type and thickness of membrane.

A more exact presentation is given by Davson and Danielli.[16]

That such considerations are important in predicting transfer of vitamin A to milk is indicated in our studies, where at corresponding blood levels the changes in milk levels were almost the same. Similar changes required three times as much vitamin A in oil I as in aqueous dispersion I. By administering six times as much vitamin A in oil I

16. Davson, H., and Danielli, J. F.: The Permeability of Natural Membranes, London, Cambridge University Press, 1943.

as in aqueous dispersion, still higher levels were obtained in blood, and greater changes in milk level followed. This certainly suggests that concentration in the blood is an important factor in determining the milk level, but this does not imply that it is the only factor involved. If such considerations are true, it should follow that one should produce maximal transfer of vitamin A to milk by injecting intravenously a given dose of vitamin A. Since maximum levels are obtained with intravenous injection, the milk levels should be higher and should reach their maximum earlier. This was indeed the case when milch cows were given (1) intravenous injections of aqueous dispersions of vitamin A, (2) oral doses of the same aqueous dispersion and (3) oral doses of the same vitamin A in oily solution (the oral administration was made through a stomach tube through which the test dose was quantitatively rinsed.) The total increase in milk vitamin A in the 48 hour collection period following the test dose was almost 10 times as great with the intravenous injection and four times as great with the aqueous dispersion given orally as with oily solution given orally.[17] The maximum rise, just as might be expected from theoretical considerations, took place much earlier with intravenous injection than with oral administration. This finding, in essence, is in harmony with the concept that the laws of diffusion are important in defining the amount and rate of transfer of vitamin A from blood to milk.

The clinical implication of this definition of the laws of transfer of vitamin A from blood to milk is important if one considers the possibility that a deficiency may exist only in one or more tissues due to impaired membranes of cell and capillary walls with which they are in contact. The intestinal membrane offers an analogous situation. Vitamin A deficiency may result whenever this membrane is defective or injured, or the chemical system necessary for fat absorption is not functioning. (Impaired intestinal absorption was found in premature and newborn infants, and patients with celiac syndrome, biliary block, liver disease, sprue, gastrectomy, diarrhea and cretinism.[10]) With such an example, one can conceive of a similar situation existing in the transfer of fat-soluble vitamins from the blood to a given tissue. This may be the reason that a wide variety of skin diseases which can be defined by the common denominator of hyperkeratosis improve on prolonged treatment with high doses of vitamin A. Dermatological abnormalities like acne vulgaris, atypical lichen planus, pityriasis, leukoplakia, xeroderma, lupus vulgaris and acanthosis nigricans have the common symptoms of vitamin A

17. Sobel, A. E.; Rosenberg, A. A., and West, M. M.: Intravenous Injections of Fat-Soluble Vitamins, in the Abstracts of Papers Read Before the One Hundred and Sixteenth Meeting of the American Chemical Society, Division of Biological Chemistry, Atlantic City, N. J., Sept. 18, 1949. Sobel, A. E., and Rosenberg, A. A.: Unpublished experiments.

deficiency. Administration of vitamin A was necessary in large doses, 200,000 to 400,000 U. S. P. units daily over considerable periods, before improvement was noted. "The consensus of opinion seemed to be that vitamin A deficiency was the cause of the skin abnormality even in those cases where the diets were analyzed and a perfectly adequate intake of vitamin A and carotene was found."[18] The high doses may be actually necessary to provide the high blood levels needed to overcome an impaired membrane system and enable vitamin A to reach the affected tissue in sufficient amount. It has been our observation,[19] at least in acne vulgaris, that earlier improvements were obtained with aqueous dispersions of vitamin A which produced higher blood levels than were reported by Straumfjord,[19] who gave twice the dose in oil and produced favorable results.

It might be added that the improved transfer to milk with aqueous dispersions is probably not limited to vitamin A. The other fat soluble vitamins, D, E and K, should behave in the same manner.

METHODS

The method employed for the estimation of vitamin A in fingertip blood plasma was that described by Bessey and his colleagues[20] with the modifications described by Sobel and his colleagues.[11] The method employed for the estimation of milk vitamin A (for 0.25 to 1.00 cc. of milk) was that of Sobel and Rosenberg.[21] Specimens, unless immediately analyzed, were sealed and placed in the freezer to prevent any changes in vitamin A content. The results were considered valid with the blood method only if (1) complete destruction of vitamin A standard in a xylene and kerosene mixture was obtained after irradiation, (2) satisfactory recovery was obtained and (3) the standard vitamin A checked the calibration chart; with the milk method only if (1) satisfactory recovery was obtained and (2) standard vitamin A after reaction with glycerin dichlorohydrin checked the calibration chart.

Determination of recovery consisted in the analysis of two samples of the same plasma or milk to one of which a known amount of vitamin A was added. This addition was in xylene and kerosene for plasma and in petroleum ether for milk.

SUMMARY

The vitamin A content of the milk and blood of human mothers was determined periodically following the administration of vitamin A in aqueous and oily mediums. The vitamin A content of human milk

18. Harris, P. L.: Fat Soluble Vitamins, Ann. Rev. Biochem. **18**:391, 1949.

19. Straumfjord, J. V.: Vitamin A: Its Effect on Acne, Northwest Med. **42**:219 (Aug.) 1943.

20. Bessey, O. A.; Lowry, O.; Brock, M. J., and Lopez, J. A.: The determination of Vitamin A and Carotene in Small Quantities of Blood Serum, J. Biol. Chem. **166**:177 (Nov.) 1946.

21. Sobel, A. E., and Rosenberg, A. A.: Vitamin A in Milk: Microestimation with Activated 1,3-Dichloro-2-Propanol, Analyt. Chem. **21**:1540 (Dec.) 1949.

underwent considerable rise within 12 hours following the administration of vitamin A in aqueous medium. The vitamin A content of human milk did not undergo a significant rise during the first 24 hours following administration of the same vitamin A in oily solution. An explanation of this difference may be offered by the higher blood levels obtained with the aqueous dispersion, indicating improved absorption as well as fulfilment of the theoretical requisites for a greater total diffusion to the site of milk production. When corresponding blood vitamin A levels are obtained with larger amounts of oily vitamin A compared to the aqueous, the transfer to milk is similar.

Dr. S. M. Gordon, of Endo Products, Inc., Richmond Hill, N. Y., prepared and supplied the various aqueous dispersions of vitamin A used in this study. Mead Johnson & Company supplied the percomorph liver oil.

This study was aided by a grant from Endo Products, Inc.

PLASMA PROTHROMBIN IN INFANTILE DIARRHEA

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THE BOWEL is the site of absorption of vitamin K and its synthesis by micro-organisms. Pathological states in the alimentary canal may therefore be reflected in a lowered plasma prothrombin level. Hypoprothrombinemia of enteral origin is known to occur in severe protracted diarrhea [1] and in several other conditions, all having in common an impairment of intestinal absorption.[2]

Interest in prothrombin in the pediatric literature has centered around hemorrhagic disease of the newborn. In older infants no marked difference in prothrombin activity from that in adults and older children has been noted. Rapoport and Dodd [3] observed a prolongation of prothrombin time in seven infants with chronic diarrhea and drew attention to the apparently not infrequent occurrence of hypoprothrombinemia in infants suffering from this condition.

Animal experiments [4] and experience with human beings [5] have shown that hypoprothrombinemia may result from the use of sulfaguani-

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1. (*a*) Mackie, T. T.: Vitamin K Deficiency in the Absence of Jaundice, New York State J. Med. **40**:987, 1940. (*b*) Warner, E. D.; Spies, T. D., and Owen, C. A.: Hypoprothrombinemia and Vitamin K in Nutritional Deficiency States, South. M. J. **34**:161, 1941.

2. Page, R. C., and Bercovitz, Z.: Prothrombin and Fibrinogen Studies in Chronic Ulcerative Colitis, Am. J. Digest. Dis. **9**:419, 1942. Kark, R., and Souter, A. W.: Hypoprothrombinemia and Avitaminosis K in Man, Brit. M. J. **2**:191, 1941. Hult, H.: Fall av sprue behandlat med K-vitamin, Nord. med. **3**:2428, 1939. Fanconi, G.: Zöliakie, Deutsche med. Wchnschr. **64**:1565, 1938. Clark, R. L.; Dixon, C. F.; Butt, H. R., and Snell, A. M.: Deficiency of Prothrombin Associated with Various Intestinal Disorders, Proc. Staff Meet., Mayo Clin. **14**:407, 1937.

3. Rapoport, S., and Dodd, K.: Hypoprothrombinemia in Infants with Diarrhea, Am. J. Dis. Child. **71**:611 (June) 1946.

4. Kornberg, A.; Daft, F. S., and Sebrell, W. H.: Production of Vitamin K Deficiency in Rats by Various Sulphonamides, Pub. Health Rep. **59**:832, 1944.

5. Lockwood, J. S.; Young, A. D.; Bouchelle, M.; Bryant, T. R., and Stojowski, A. J.: Appraisal of Oral Streptomycin as an Intestinal Antiseptic, with Observations on Rapid Development of Resistance of E. Coli to Streptomycin, Ann. Surg. **129**:14 (Jan.) 1949.

dine, succinylsulfathiazole and orally administered streptomycin. These locally acting "intestinal antiseptics," in common use in the treatment of diarrhea, may lower the plasma prothrombin level by exerting their bacteriostatic and bactericidal action on the intestinal flora engaged in the synthesis of vitamin K.

The present study deals with plasma prothrombin in acute gastrointestinal disturbances in infants and with the effect of sulfaguanidine, succinylsulfathiazole and orally administered streptomycin on the prothrombin level under these conditions.

MATERIAL AND METHODS

Serial prothrombin determinations were done at regular intervals on 21 infants with acute gastroenteritis. The patients in this series were not selected for severity or long duration of their disease or for any other criteria. Every patient admitted to the ward during the summer and autumn of 1949 was regarded as eligible for this study, however mild the disease was.

Eight patients (cases 1 to 8) were regarded as having "fresh" disease, occurring in previously apparently well infants. All but two patients (cases 6 and 7) recovered. The fatal cases will be reported in detail. Thirteen patients (cases 9 to 21) had acute episodes of diarrhea against a background of malnutrition. The histories of these children include previous episodes of gastroenteritis and parenteral infection.

Five patients (cases 9 to 13) did not receive any chemotherapy. All other patients were given "intestinal antiseptics," that is sulfaguanidine, succinylsulfathiazole and orally administered streptomycin, alone or in combination. Their effect on the prothrombin level will be discussed later. An evaluation of these drugs in infantile diarrhea is outside the scope of this paper.

The material included 10 cases of diarrhea due to Shigella and 11 of "nonspecific" diarrhea, that is, cases in which no etiological factor could be found. Parenteral infection, mostly otitis media, was present in seven cases.

It is our routine in cases of diarrhea to start oral feeding after 24 hours. A half-skim or protein milk formula is given in quantities of 180 to 200 ml. in the first 24 hours and increased by 120 to 180 ml. daily. Fluids, blood and plasma, are given to correct dehydration and acidosis.

Prothrombin determinations were done with the one stage method of Quick on oxalated venous blood, with use of fresh saline extract of Difco rabbit-brain thromboplastin. Two milliliters of blood were obtained from the femoral vein, jugular veins or superior longitudinal sinus. Prothrombin percentages were calculated by plotting prothrombin times on a standard curve obtained from saline dilutions of normal plasma.

Brinkhous, Smith and Warner,[6] using a two stage method, found the normal prothrombin concentration to be low in early infancy, gradually rising from values of 14 to 39 per cent at birth and approaching normal adult levels toward the end of the first year of life. Prothrombin activity

6. Brinkhous, K. M.; Smith, H. P., and Warner, E. D.: Plasma Prothrombin Level in Normal Infancy and in Hemorrhagic Disease of the Newborn, Am. J. M. Sc. **193**:475 (April) 1937.

as measured with the one stage method of Quick was found, however, to be near 100 per cent throughout infancy, with the exception of the first few days of life.[7] In the majority of our cases values around 100 per cent were reached during recovery from gastroenteritis. These values, together with similar results of prothrombin determinations done on three patients not suffering from gastroenteritis, served as controls.

RESULTS

The results are summarized in table form. It will be seen that with one exception (case 8) the initial prothrombin value was lowered in every case in this series, including the cases of mild diarrhea and those in which the diarrhea was of short duration prior to the first determination. The average initial prothrombin value for the whole series was 52 per cent. It is interesting to note that levels as low as 34 per cent may be reached in mild acute diarrhea, as in case 9.

In general, the prothrombin level corresponded to the course of the diarrhea. Recovery was accompanied with a return of the prothrombin value to normal, whereas in the two fatal cases (cases 6 and 7) the gradual downhill course was reflected in the steady fall in prothrombin levels. In four of the 13 chronically malnourished infants in this series the prothrombin level remained low during the entire period of observation, even after the acute diarrhea had subsided.

Although the prothrombin levels in the average case in this material are well above the danger line of bleeding tendency, values as low as 12.5 per cent (case 13), 17 per cent (case 6) and 16 per cent (case 7) were encountered. In the last case there was severe hemorrhage. This observation suggests that hypoprothrombinemia in infantile diarrhea may be of more than academic interest and should be taken into consideration in the practical management of cases.

The fall in prothrombin did not appear to be due to sulfaguanidine, succinylsulfathiazole or streptomycin. This is evident from the fact that equally low prothrombin values were observed in the patients not receiving these drugs. In the patients receiving chemotherapy low prothrombin levels were found present at the first determination, done before chemotherapy was started. Furthermore, the prothrombin level was observed to rise while the patients were actually under sulfaguanidine, succinylsulfathiazole or oral streptomycin medication.

No difference was observed between the prothrombin levels in diarrheas due to Shigella and those of the nonspecific diarrheas. Likewise, the prothrombin level seemed to be equally affected whether the diarrhea was caused by enteral or parenteral infection.

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7. Owen, C. A.; Hoffman, G. R.; Ziffren, S. E., and Smith, H. P.: Blood Coagulation During Infancy, Proc. Soc. Exper. Biol. & Med. **41**:181, 1939.

Case No.	Age, Months	Weight on Admission, Gm.	Stool Culture	Clinical Features	"Intestinal Antiseptics"	Prothrombin per Cent and Days in Hospital *										Remarks
1	11	7,600	Negative	Diarrhea and vomiting; dehydration and acidosis	Oral streptomycin, 0.5 Gm.	42 (4)	52 (5)	45 (8)	50 (12)	100 (16)	.....	.....	.....	.....	.....	.....	.....
2	22	10,300	Negative	Diarrhea +++; dehydration and acidosis	Oral streptomycin, 0.5 Gm.	54 (2)	47 (4)	69 (6)	75 (8)	100 (9)	.....	.....	.....	.....	.....	.....	(Chart 3)
3	2	4,700	S. flexneri	Diarrhea and dehydration	Oral streptomycin, 1 Gm.; succinyl-sulfathiazole	56 (2)	56 (4)	100 (6)	100 (11)	.....	.....	.....	.....	.....	.....	.....	.....
4	18	9,650	S. flexneri	Moderate diarrhea	Succinylsulfathiazole	46 (4)	54 (6)	100 (8)	100 (15)	.....	.....	.....	.....	.....	.....	.....	(Text)
5	14	8,800	S. flexneri	Dysentery, severe; temperature 40 C. (104 F.) on admission	Oral streptomycin, 1 Gm.	50 (2)	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....†
6	6	6,700	Negative	Acute gastroenteritis with dehydration; otitis media and mastoiditis; urinary tract infection	Oral streptomycin, 0.5 Gm.	62 (6)	50 (8)	47 (6)	30 (12)	28 (14)	18 (16)	24 (17)	27 (19)	17 (21)	.....	.....	Died; (chart 4)
7	9	6,450	S. flexneri	Dehydration and acidosis, severe; purpura and intestinal hemorrhage	Oral streptomycin, 0.5 Gm.; succinyl-sulfathiazole	50 (2)	29 (4)	30 (5)	28 (7)	31 (9)	22 (11)	16 (14)	.....	.....	.....	.....	Died; (chart 5)
8	8	6,950	S. flexneri	Stools, blood and mucus; excellent general condition	Oral streptomycin, 0.5 Gm.; succinyl-sulfathiazole	100 (6)	100 (8)	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
9	9	6,250	Negative	Diarrhea; weight loss; bilateral otitis media	.....	34 (2)	66 (5)	100 (7)	.....	.....	.....	.....	.....	.....	.....	.....	.....
10	5	5,750	Negative	Acute diarrhea; active rickets; otitis media	.....	39 (4)	62 (7)	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
11	12	6,970	Negative	Diarrhea; vomiting; anorexia	.....	58 (1)	46 (3)	100 (7)	.....	.....	.....	.....	.....	.....	.....	.....	(Chart 1)
12	12	6,700	Negative	Acute gastroenteritis; malnutrition	.....	44 (3)	70 (5)	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
13	2	3,100	Negative	Vomiting; weight loss	.....	17 (1)	12.5 (2)	68 (3)	70 (4)	100 (7)	100 (12)	100 (21)	.....	.....	.....	.....	.....‡
14	6	4,150	Negative	Acute gastroenteritis; otitis media	Oral streptomycin, 1 Gm.; succinyl-sulfathiazole	63 (2)	80 (6)	100 (9)	.....	.....	.....	.....	.....	.....	.....	.....	.....
15	7	4,500	S. flexneri	Diarrhea; dehydration ++	Oral streptomycin, 0.5 Gm.; sulfaguanidine	65 (26)	50 (28)	54 (21)	100 (37)	100 (39)	.....	.....	.....	.....	.....	.....	.....
16	9	5,450	(1) Negative (2) S. flexneri	Malnutrition; nonspecific gastroenteritis; later, dysentery (ward infection)	Succinylsulfathiazole	56 (2)	53 (3)	100 (5)	90 (7)	100 (9)	100 (10)	54 (24)	58 (28)	100 (32)	.....	.....	(Chart 2)
17	4	4,250	Negative	Diarrhea ++; vomiting; bilateral otitis media	Succinylsulfathiazole	60 (4)	50 (8)	56 (11)	42 (14)	.....	.....	.....	.....	.....	.....	.....	.....§
18	3	3,450	S. shigae	Dehydration; diarrhea mild	Oral streptomycin, 0.5 Gm.; succinyl-sulfathiazole	40 (11)	47 (14)	57 (16)	61 (18)	73 (20)	62 (23)	66 (31)	58 (33)	.....	.....	.....	.....
19	1½	3,900	Negative	Diarrhea and dehydration on admission; otitis media; cleared up in 2d week	Succinylsulfathiazole	62 (1)	58 (3)	60 (5)	52 (7)	60 (10)	57 (18)	62 (26)	62 (29)	55 (32)	66 (35)	53 (38)	.....
20	12	8,230	S. ambigua (Schmitz)	Diarrhea mild; infectious lymphocytosis	Sulfaguanidine	60 (2)	75 (4)	56 (6)	46 (12)	60 (14)	.....	.....	.....	.....	.....	.....	.....
21	18	6,250	S. flexneri	Mild diarrhea; worse in 2d week	Oral streptomycin, 0.5 Gm. sulfaguanadine	62 (1)	80 (7)	66 (9)	54 (13)	57 (17)	68 (21)	54 (30)	.....	.....	.....	.....	.....

* Figures in parentheses refer to days in hospital.
† Measles rash on 3d day; transferred to fever hospital.
‡ Received menadione sodium bisulfite; (text).
§ H. influenzae meningitis on 14th day.

In addition to the summary information contained in the table, seven cases are presented in detail. Four are representative of the various groups within the material. Three are of special interest and cannot be dealt with adequately in table form.

REPORT OF CASES

Case 11 (chart 1).—A 1 year old infant, in good general condition, was admitted with a history of diarrhea and vomiting of one day's duration. The stool culture was negative for Shigella and Salmonella.

Oral milk feeding was withheld for 12 hours. No chemotherapy was given. The diarrhea improved on the first day, and the stools remained normal throughout hospitalization. From the sixth day onward there was steady gain in weight.

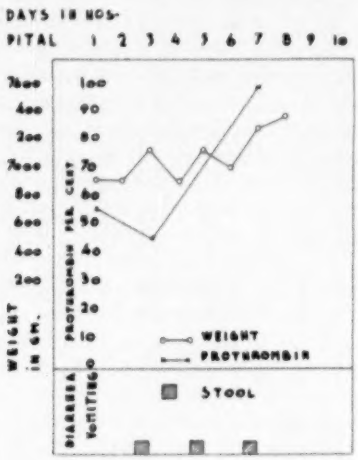

Chart 1 (case 1).—Clinical record of a 1 year infant.

The prothrombin level, which was 58 per cent on admission and 46 per cent on the third hospital day, reached 100 per cent on the seventh day.

Case 16 (chart 2).—A 9 month old girl, weighing 5,450 Gm., was admitted with a history of diarrhea for 10 days. Stool cultures did not yield pathogens. The prothrombin level was 56 per cent on admission. Succinylsulfathiazole administration was started on the second day and continued for nine days. As the diarrhea improved, the prothrombin level rose; it was found to be 100 per cent on the fifth day and again on the tenth day.

During the third week in the hospital diarrhea, vomiting and weight loss recurred. On this occasion Shigella flexneri was cultured from the stools. A new series of prothrombin determinations was started which revealed a lowered prothrombin level of 54 per cent. Succinylsulfathiazole was given again. As the diarrhea subsided and the weight curve began to rise, the prothrombin returned to the 100 per cent level.

Case 2 (chart 3).—A 22 month old, well developed boy was admitted with a history of watery diarrhea and vomiting of five days' duration. On admission

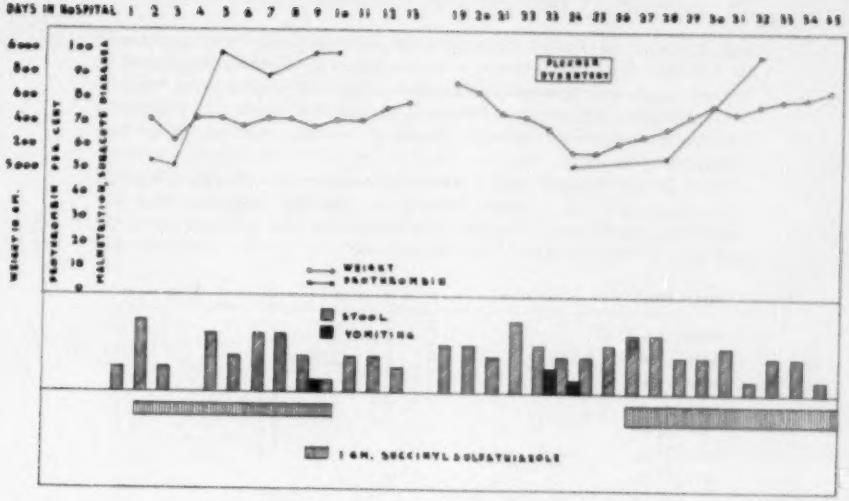

Chart 2 (case 16).—Clinical record of a 9 month old girl.

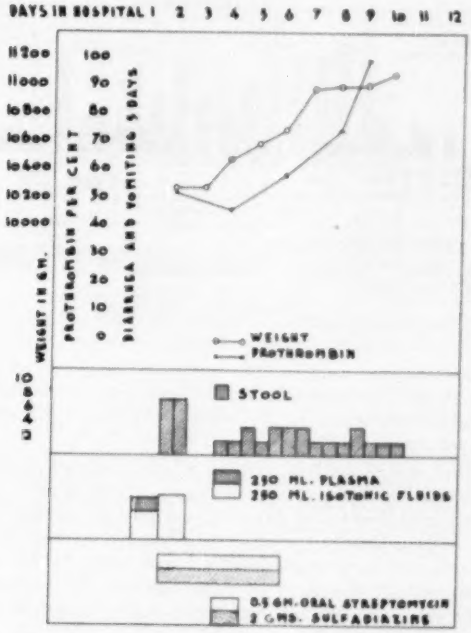

Chart 3 (case 2).—Clinical record of a 22 month old boy.

there was severe dehydration and acidosis, and fluids were administered parenterally for two days. Oral administration of streptomycin and sulfadiazine was started on the second day and continued for five days. The child made a rapid recovery. The prothrombin level on admission was 54 per cent, and despite the streptomycin it gradually increased parallel with the patient's recovery, reaching 100 per cent on the ninth day.

CASE 4.—An 18 month old boy entered the hospital with a history of diarrhea with mucous stools for a period of four weeks preceding admission. The stool culture was positive for S. flexneri. The mucous diarrhea continued during the first week of hospitalization. The prothrombin level on the fourth day was

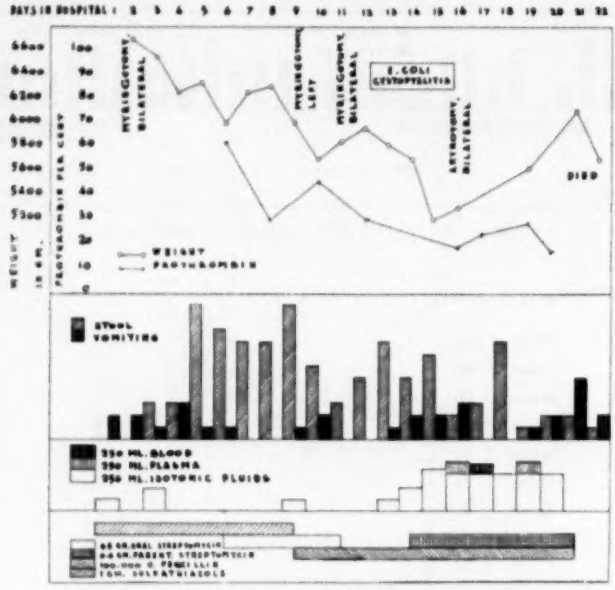

Chart 4 (case 6).—Clinical record of a 6 month old girl.

46 per cent. Succinylsulfathiazole was given on the fifth day and the administration continued for 14 days. Simultaneous with the improvement of the diarrhea and despite the succinylsulfathiazole, the prothrombin level rose to 100 per cent and was still 100 per cent on the fifteenth hospital day.

CASE 6 (chart 4).—A 6 months old girl, who had had measles three weeks previously, was admitted with a two day history of vomiting, diarrhea and weight loss. Bilateral otitis media was diagnosed, and marked vomiting during the first few days of hospitalization was apparently due to the ear condition. Toward the end of the first week of hospitalization a severe watery diarrhea which was not affected by orally administered streptomycin developed. The weight curve went down steadily, and during the first two weeks in the hospital the child lost

1,500 Gm. In the second week a urinary infection with a streptomycin-resistant strain of Escherichia coli was found.

Since the otitis after myringotomy responded neither to streptomycin nor to penicillin, it was decided on the sixteenth hospital day to perform an antrotomy.

After the operation, signs of incomplete intestinal obstruction were present: distended abdomen, infrequent bowel movements and vomitus containing bile. The child died on the twenty-second hospital day. At necropsy an area of hemorrhagic infarction was found in the small bowel.

Concurrent with the weight curve, the prothrombin curve dropped steadily to values below the 20 per cent level. A slight rise in the prothrombin level was

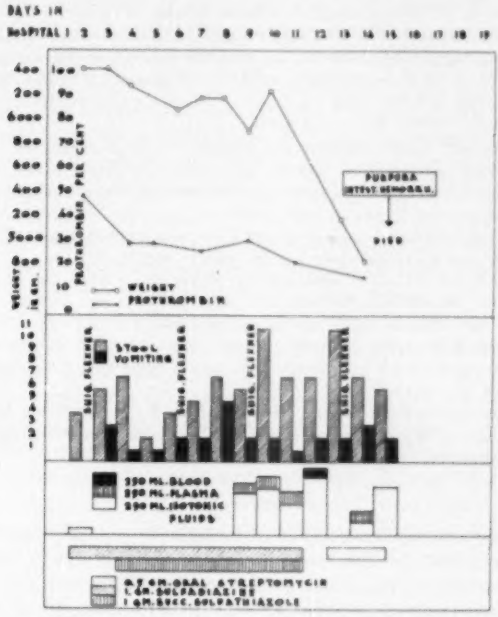

Chart 5 (case 7).—Clinical record of a 9 month old girl.

observed following plasma and blood transfusions, but this rise was temporary, and before death the prothrombin estimation was again down to 17 per cent. No clinical manifestations of bleeding were seen in this case.

Case 7 (chart 5).—A 9 month old girl, ill with measles three weeks previously, had progressively severe diarrhea for 10 days before admission. On admission, there was a moderate degree of dehydration. The skin was loose, but in spite of this evidence of recent weight loss the child was alert and did not appear seriously ill. The stools were loose, containing mucus, and the culture yielded S. flexneri.

The child received a subcutaneous infusion of isotonic sodium chloride solution. Graded oral feeding with a half-skim milk formula was started the following day.

Sulfadiazine was given from the day of admission onward, and succinylsulfathiazole was added on the third day.

Diarrhea and vomiting increased toward the end of the first week in the hospital, and the child again became dehydrated. Oral feeding was stopped, and fluids, including plasma and blood, were given by intravenous drip. Hydration could not be maintained, however, in spite of continuous intravenous therapy, and the weight curve went down rapidly. The Shigella infection was resistant to the sulfonamides, and the stool culture was still positive for S. flexneri on the thirteenth day. The diarrhea did not improve, and administration of streptomycin orally was started on the thirteenth day.

The prothrombin level was 50 per cent on admission and showed a progressive fall parallel to the weight curve. It reached a level of 16 per cent on the day before death, despite the fact that the child received plasma and blood transfusions for the preceding six days with but one exception. The following day a purpuric rash appeared on the trunk and limbs, and there was a massive intestinal hemorrhage. The child died in acute anoxemia before a blood transfusion could be started. Permission for autopsy was not obtained.

Case 13.—A 9 week old girl was admitted from an immigrant camp, for persistent vomiting, recurrent diarrhea and weight loss over a period of several weeks. She was in a poor state of nutrition, and her weight on admission was 3,200 Gm.

In the hospital diarrhea was not severe. There was a tendency toward vomiting; the appetite was poor, and there was no gain in weight.

The prothrombin level on admission was 17 per cent. When the determination was repeated the following day the level was 12.5 per cent. In view of these low values and although there was no clinical evidence of bleeding, a vitamin K analog, menadione sodium bisulfite (hykinone®), 9.6 mg. daily, was given intramuscularly for three consecutive days, with a rapid rise in the prothrombin level to 100 per cent.

The prothrombin level was still 100 per cent on the thirteenth and twenty-first days, although no marked change in the child's condition had taken place; there was still occasional vomiting and only slight weight gain.

COMMENT

Hypoprothrombinemia of enteral origin is generally attributed to interference with the absorption of vitamin K. This may be due either to hypermotility of the bowel or to qualitative and quantitative changes in the absorptive capacity of its mucosa. Hypermotility operates in diarrhea. Malabsorption is present in sprue, celiac syndrome, ulcerative colitis and intestinal fistulas.

It appears to my co-workers and me that the hypoprothrombinemia encountered in our cases cannot be adequately explained on the basis of these mechanisms alone and that interference with the formation of vitamin K in the bowel by micro-organisms is mainly responsible. Far reaching qualitative and quantitative changes in the intestinal flora as well as in its milieu are associated with diarrhea. The synthesis of vitamin K may quite conceivably suffer under these altered conditions. Especially in infancy, we believe, this factor is of primary importance in the genesis of hypoprothrombinemia. Dietary vitamin K is supplied

chiefly by green leaves. Animal sources are relatively poor in this material, and milk, which is the only or main item in the infant's diet, especially during the first few months of life, contains only minimal and varying amounts of preformed vitamin K.[8] The infant, therefore, depends largely on intestinal synthesis for his supply of vitamin K. The same applies even more strongly to the infant suffering from diarrhea, whose diet after an initial period of complete starvation consists of diluted or modified milk in insufficient amounts over varying periods. The amounts of vitamin K supplied to the diarrheal infant in his diet are therefore negligible. If the other source of vitamin K, that is, intestinal synthesis, fails, hypoprothrombinemia will result.

In addition to these enteral changes, liver damage may operate as a factor in the production of hypoprothrombinemia in infantile diarrhea. This is particularly true in infants with severe diarrhea. Little information is available on the subject of liver damage in diarrheal disease, its incidence and pathogenesis. Six cases of gastroenteritis in infants with clinical evidence of liver damage were recently reported by Schlesinger, Payne and Burnard.[9] No such evidence was found in our material. We excluded liver damage in case 13, in which parenteral administration of a vitamin K analogue was followed by a prompt rise in the prothrombin level. Vitamin K was not given to the other two patients with very low prothrombin levels, and no further opportunities for testing the prothrombin response to parenterally administered vitamin K presented themselves later in the study.

The four chronically malnourished infants whose prothrombin levels remained low after the acute diarrhea had subsided may have had a permanently low prothrombin level independent of the diarrhea. This series is far too small to permit any conclusions. It may, however, be tentatively suggested that chronic malnutrition in infancy might in itself constitute a cause for a moderate hypoprothrombinemia, possibly owing to inefficient utilization of vitamin K.[1b] Malabsorption may be present in these cases even in the absence of any signs of acute diarrhea. The factor of liver damage can also not be ruled out in chronic malnutrition.

A point of importance brought out by this study is the observation that the prothrombin level is not affected by sulfaguanidine, succinylsulfathiazole and orally administered streptomycin. This finding was unexpected, as it apparently contradicted theoretical considerations, results of animal experiments [4] and practical experience with surgical patients.[5] This apparent discrepancy can, however, be accounted for, as on closer examination it is evident that our material, on the one hand,

8. Bicknell, F., and Prescott, F.: The Vitamins in Medicine, ed. 2, New York, Grune & Stratton, Inc., 1946.

9. Schlesinger, B.; Payne, W. W., and Burnard, E. D.: Liver Damage in Gastro-Enteritis, Arch. Dis. Childhood **24**:15 (March) 1949.

and the experimental animals or the preoperative patients, on the other hand, do not constitute comparable groups. Whereas in the latter two groups there were normal or near normal intestinal floras and prothrombin concentrations when the use of sulfonamide or oral streptomycin was started, in our material the starting point was an already disturbed flora and lowered prothrombin level. A further lowering of the prothrombin level as a result of the concurrent action of the chemotherapeutic agents is not necessarily the only outcome to be expected in these circumstances. Within the wide range of factors acting on the prothrombin level in diarrhea, the effect of the sulfonamides and streptomycin does not assert itself in the over-all picture. Inasmuch as these drugs are effective in the treatment of the diarrhea, they might even help raise the prothrombin level by helping in the restoration of a normal flora in the bowel.

SUMMARY

Serial prothrombin determinations were carried out in 21 infants with acute diarrhea of varying degrees of severity. The prothrombin level was found to be lowered during the attack of diarrhea in all cases but one. The average prothrombin level on the first determination was 52 per cent, and the lowest value encountered, 12.5 per cent of normal.

The course of the diarrhea was generally reflected in the prothrombin level, which rose and reached normal values parallel to recovery from the diarrhea or went down steadily in the fatal cases. In four cases of acute diarrhea in chronically malnourished infants the prothrombin level remained low even after recovery from the acute attack of diarrhea.

Sulfaguanidine, succinylsulfathiazole and orally administered streptomycin were given in 16 cases. The prothrombin level did not appear to be affected by these agents, its level being determined by the diarrhea per se.

Factors operating in the genesis of hypoprothrombinemia in diarrhea are discussed, and the importance of interference with the intestinal synthesis of vitamin K in infants is emphasized.

Case Reports

DURATION OF ACUTE LEUKEMIA IN CHILDREN

Review of the Literature and Report of a Case of Unusually Long Survival

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AND
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This report considers the duration of leukemia in children and reports the unusually long survival period of twenty months in an infant aged 19 months at the onset. Unusually long survival in leukemia has been reported several times in the past. The diagnoses in these cases have been qualified by a variety of terms such as "atypical," "subacute" and "chronic." Apparently there is no generally accepted term applied to prolonged leukemia in children.

In 1933, Cooke [1] suggested that the term "chronic lymphoid leukemia" be applied to the disease as it typically exists in adults with the usual criteria of prolonged course, excessive splenomegaly, enlargement of lymph nodes and presence in the blood and bone marrow of large numbers of small lymphocytes, but without early thrombopenia, hemorrhagic tendencies or a rapidly developing anemia. He suggested that cases of lymphatic leukemia in children with prolonged survival be considered as variants of acute leukemia. He admitted that chronic myelogenous leukemia occurs in children but is relatively rare.

In a recent review of cases of chronic lymphoid leukemia in children, Holowach [2] observed that the cases reported up to that time met the generally accepted diagnostic criteria of acute leukemia with some variation but did not resemble chronic lymphoid leukemia of adults. Holowach did report on 1 patient, still living at the time of the report, whose condition resembled the adult disease.

From May 1928 until January 1949, 48 children with leukemia were admitted to the Strong Memorial and Rochester Municipal Hospitals, Rochester, N. Y. Since the etiology, symptomatology and diagnostic signs and laboratory procedures relative to the disease have been discussed in detail in other reports,[3] only certain

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1. Cooke, J. V.: Acute Leukemia in Children, J. A. M. A. **101**:432 (Aug. 5) 1933.

2. Holowach, J.: Chronic Lymphoid Leukemia in Childhood, J. Pediat. **32**:84, 1948.

3. (*a*) Cooke.[1] (*b*) Ramsay, G. W. S. C.: Leukemia in Infancy and Early Life, Arch. Dis. Childhood **2**:119, 1927. (*c*) Abt, A. F.: The Diagnosis of Leukemia in Childhood, M. Clin. North America **21**:89, 1937. (*d*) Craver, L. F.: Lymphomas, Leukemias and Allied Disorders in Children, J. Pediat. **15**:332, 1939. (*e*) Simonson, L. M.: Acute Leukemia in Childhood: An Analysis of Sixteen Cases, Wisconsin M. J. **37**:110, 1938. (*f*) Cooke, J. V.: The Incidence of Acute Leukemia in Children, J. A. M. A. **119**:547 (June 13) 1942. (*g*) Mills, S. D.: Acute Lymphatic Leukemia in Childhood, J. Pediat. **6**:634, 1935. (*h*) Falkenstein, D., and Fowler, W. M.: Acute Lymphatic Leukemia in Childhood, Am. J. Dis. Child. **65**:445 (March) 1943. (*i*) Dale, J. H., Jr.: Leukemia in Childhood, J. Pediat. **34**:421, 1949.

TABLE 1.—*Data on Children with Leukemia*

Number of patients	48
Date of death known	44
Longest survival	20 mo.
Shortest survival	1 week
Average survival	3.5 mo.
Sex Incidence	**No. of Patients**
Male	26
Female	22
Race	
White	47
Negro	1
Age, Yr.	
0 to 1	1
1 to 2	4
2 to 3	8
3 to 4	10
4 to 5	4
5 to 6	4
6 to 7	3
7 to 8	2
8 to 9	1
9 to 10	3
10 to 11	3
11 to 12	0
12 to 13	1
13 to 14	3
14 to 15	1

Age to Sex Ratio

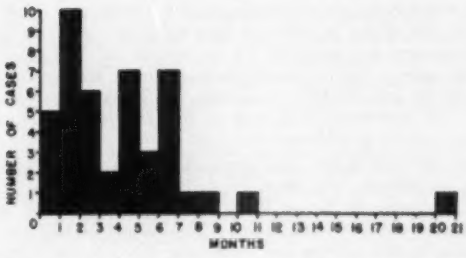
Age, Yr.	Boys	Girls
0 to 5	15	15
5 to 10	7	5
10 to 15	1	1

TABLE 2.—*Data on Symptoms and Signs in Children with Leukemia*

Symptoms	Number	Percentage
Fever	41	85
Pallor	36	75
Bleeding manifestations	20	42
Bone and joint pain	17	35
Sore throat	11	23
Cough	1	
Signs		
Pallor	42	87
Purpura	38	80
Fever	34	71
Gingivitis or stomatitis	14	30
Tonsillitis or pharyngitis	4	8
Lymph node enlargement	37	78
Slight	18	37
Moderate	15	31
Great	4	8
Hepatic enlargement	41	85
Slight	20	42
Moderate	20	42
Great	1	..
Splenic enlargement	39	81
Slight	13	27
Moderate	16	33
Great	10	21

TABLE 3.—*Laboratory Findings on the Hospital Admission of Children with Leukemia*

	Number	Percentage
White blood cell count		
10,000 or below	18	58
Above 10,000	20	42
Thrombocytes reduced	35	73
Types		
Lymphoid	42	97
Myeloid	3	..
Monocytic	1	..
Undifferentiated	2	..
Average red blood cell count		2,300,000
Average hemoglobin concentration		6.2 Gm./100 Cc.
Roentgenographic changes in long bones		
Positive	13	40
Negative	19	60
Not taken	16	..



Graph showing length of survival in patients with leukemia.

data from our cases have been summarized in tables 1, 2 and 3 and in the figure. Except for the case reported, the survival period from apparent onset of symptoms until death was under one year.

REPORT OF CASE

M. B., a 19 month old white girl, was admitted to Strong Memorial Hospital on April 22, 1947. The chief complaint was pallor of seven weeks' duration. This was associated with slight fatigue and anorexia. Two days prior to her admission she had a mild nasal discharge and appeared more pale and listless. There was no history of bleeding or of purpura. The diet was adequate. The past and family histories were not contributory. On her admission the temperature was 38 C. (100.4 F.), the pulse rate 140 per minute and respirations 24 per minute. She appeared to be of normal development, well nourished, alert and comfortable, but chronically ill. The skin was definitely pale with a lemon yellow tint. No purpura or rash was observed. The inguinal and cervical nodes were the size of peas, discrete but not firm, while those in the axillas were not palpable. The oral mucous membranes were pale and not inflamed. The heart was normal in size; but the sounds were exaggerated, and a loud systolic murmur was audible over

the entire precordium. The edge of the liver extended 2 cm. below the left costal margin; the spleen and kidneys were not palpable. The results of the remainder of the physical examination were normal.

The blood Wassermann reaction was negative. On her admission, the red blood cell count was 1,110,000, the hemoglobin content 3.5 Gm. and the white blood cell count 4,100, with 50 per cent neutrophils, 45 per cent lymphocytes, 5 five per cent monocytes and no eosinophils or basophils. There were no abnormal leukocytes, and the thrombocytes were considered to be abundant. The red blood cells revealed slight anisocytosis. The specimens of urine and stool showed no abnormality. The tuberculin and Schick reactions were negative. Roentgenograms of the chest and bones of the extremities were normal. A sternal biopsy specimen was examined by members of the Division of Hematology and of the Department of Pathology. In their opinion a decided preponderance of small lymphocytes indicated a probable diagnosis of lymphatic leukemia. Hypoplastic anemia was considered to be a second possibility.

The patient was given two small transfusions and injections of 1 cc. of a purified liver extract (reticulogen®) daily for five days. Following this, there was a reticulocyte response up to 2.6 per cent and a concomitant rise of the red blood cell count and hemoglobin concentration to 3,300,000 and 9.3 Gm., respectively. This was followed by a subsequent fall for three days, after which time the patient received 30 mg. of folic acid daily by mouth for twelve days. Again the reticulocyte count rose slowly to 3.3 per cent on the eighth day of therapy, and there was again a rise in the red blood cell count and hemoglobin concentration to 3,700,000 and 10.5 Gm., respectively, on the day of her discharge from the hospital. The patient was discharged on May 23, 1947, with instructions that 10 mg. of folic acid be given three times daily.

The patient did well on folic acid therapy for two months, at which time this therapy was discontinued. On about September 1 she again became pale and listless. On September 20 the red blood cell count was 2,700,000 and she was readmitted to the hospital for transfusion. The findings on this admission were similar to those on the previous one. The skin was pale but without signs of purpura. The lymph nodes, liver and spleen were not enlarged. The temperature was 37.5 C. (99.5 F.). At this time the red blood cell count was 2,700,000, the hemoglobin concentration 8 Gm. and the white blood cell count 7,500, with 8 per cent neutrophils, 88 per cent lymphocytes and 4 per cent monocytes. The specimens of urine and stool were normal. The thrombocyte count was 90,000 per cubic millimeter. A biopsy specimen of sternal bone marrow revealed the cells to be almost all of the lymphocytic series, the great majority being stem or blast cells. After reviewing the sections of this biopsy specimen, members of the hematology and pathology departments expressed confidence in their diagnosis of lymphatic leukemia. The roentgenographic appearance of the long bones remained normal.

She was readmitted to the hospital November 10 because of progressive anemia. For the first time it was noted by her parents that she seemed to bruise easily. In the meantime, she had received folic acid and liver extract but her condition no longer responded to this therapy. Bruises were noted in the skin. The spleen extended 2 to 3 cm. below the left costal margin. At this time the white blood cell count was 5,400, with 95 per cent lymphocytes. Thrombocytes were scarce.

In December 1947 there was puffiness of the eyelids, and the cervical, axillary and inguinal lymph nodes were the size of almonds. The spleen was stony hard and extended 10 cm. below the left costal margin. The border of the liver extended 4 cm. below the right costal margin. The white blood cell count had increased to 34,300, with 90 per cent lymphocytes.

In January 1948 fever developed and she had pain in both knees and limped. The eyelids became more swollen and bluish, probably from subcutaneous hemorrhage. She received daily roentgen irradiations of 13 r for four days to each of the following areas: the upper right part of the chest, posterior portion of the chest, anterior and posterior parts of the abdomen. This therapy was discontinued because of a progressive fall in the white blood cell count to a level of 900 on January 13. Following cessation of therapy the white blood cell count rose slightly to 1,250 on the day of her discharge. In March she received another ten day course of roentgen therapy of 13 r daily and again this therapy had to be discontinued because of leukopenia.

During March, April and May she was admitted approximately every two weeks for transfusions. A purulent otitis media and pneumonia of unexplained cause developed during this period.

On June 10 swelling and tenderness of the right elbow were noted. The elbow joint was aspirated a week later and thick yellow pus was obtained, which on smear showed 90 per cent polymorphonuclear leukocytes and which on culture grew Staphylococcus aureus hemolyticus. Aspiration was followed by incision and drainage of the right elbow joint and penicillin therapy, to which she responded well.

In July she received a course of treatment with "aminopterin," 0.5 mg. daily for seven days and 1 mg. daily for three days. There was a change in the white blood cell differential count during this course from a total of 1,200, with 100 per cent lymphocytes at the onset, to 2,040, with 56 per cent lymphocytes, 38 per cent neutrophils, 1 per cent monocytes and 5 per cent stab cells at the termination of therapy.

On September 13 she had sudden onset of thick speech and inability to use the right arm. These symptoms gradually cleared in a few days. She again received high voltage roentgen therapy to the chest for a total of two daily doses of 13 r each. On September 22 she had cellulitis of the thigh, which was later surgically drained. In addition to penicillin she received 1 mg. of "aminopterin" intramuscularly daily for three days.

Prior to her final admission, on October 31, she had been bleeding from the nose and mouth for one week, had a high fever and a loose cough, and had gradually become unresponsive. She appeared emaciated and extremely pale and listless. There were edema of the legs, severe stomatitis, coarse rhonchi throughout the chest, a harsh systolic murmur over the precordium and enlarged, firm liver and spleen. A blood culture grew Staph. aureus hemolyticus. She had severe respiratory distress and died the following day.

Autopsy Observations (performed by Dr. William Wilt on Nov. 1, 1948, about three hours post mortem).—General Appearance: The skin was pale and pinhead petechiae were noted on the cheeks and arms. There was a bloody discharge from the corners of the mouth. The lymph nodes were generally small and firm. The peritoneal and pleural cavities contained no fluid, while the pericardial cavity contained 30 cc. of clear amber fluid. Matted lymph nodes were palpable in the mediastinum but did not seem to be obstructing the esophagus or trachea by pressure.

Heart: The organ weighed 100 Gm. and was considered to be normal except for petechial hemorrhages over the surface of the epicardium.

Lungs: The left weighed 170 Gm. and the right 160 Gm. There were pinhead petechial hemorrhages over the pleural surfaces. On section firm red areas were seen which stood out on the cut surface.

Spleen: The organ weighed 240 Gm. The surface was smooth and the color was a homogeneous purplish red. Trabeculae and malpighian bodies were poorly defined.

Gastrointestinal Tract: This was normal except for ileoileal intussusception for 5 cm. in the midileum but without redness of the surface or occlusion of blood vessels. It was thought to be terminal.

Pancreas: The pancreas was normal.

Liver: This organ weighed 880 Gm. and appeared grossly normal.

Adrenal Glands: The adrenal glands were normal.

Kidneys: Each kidney weighed 180 Gm. There was perirenal hemorrhage with the capsule raised 1 mm. from the surface by clotted blood. The parenchyma was pale and pink and appeared swollen and soft. The cortex was poorly made out and the glomeruli could not be identified. The calyxes, pelves and ureters appeared normal.

Pelvic Organs: There were pinhead petechiae in the trigonal mucosa of the bladder.

Bone Marrow: The marrow appeared deep red, cellular and abundant.

Brain: This weighed 1,050 Gm. There was a 2 to 3 mm. layer of blood overlying the parietal lobe in the subdural space and the subarachnoid space also contained blood. Pinhead petechiae were scattered over the brain surface.

Histologic Observations.—Heart: There were accumulations of lymphocytes and a few neutrophils and fragmented cells in the subendocardial and subepicardial areas. Small focal hemorrhages were seen in the same areas. A diffuse hemorrhage into a papillary muscle was noted.

Lungs: There were lymphocytic infiltrations around the vessels and bronchi. In some areas the alveoli contained blood. A section through a hilar lymph node showed congestion of sinusoids by large macrophages filled with red cells. The parenchyma consisted solely of lymphocytes, among which was deposited a great amount of golden brown pigment.

Spleen: Sinusoids were filled with lymphocytes and the pulp areas were entirely composed of lymphocytes. Golden brown pigment was seen in some quantity in the phagocytic cells.

Gastrointestinal Tract: The mucosa was heavily infiltrated with lymphocytes. Small areas of hemorrhage into the mucosa were seen.

Liver: There was prominent infiltration of the portal areas and sinusoids by lymphocytes. The hepatic cells contained large amounts of golden brown pigment within the cytoplasm. There was pronounced perivascular lymphocytic cuffing. Dense lymphocytic infiltration was seen in the wall of the gallbladder. A lymph node in the region of the gallbladder contained phagocytic cells with golden brown pigment, and the capsule of the node was infiltrated with lymphocytes.

Pancreas: This organ was normal.

Adrenal Glands: These were normal except for heavy lymphocytic infiltration of the adjacent connective tissue.

Kidneys: There was extensive lymphocytic infiltration of the intertubular ground substance in both cortex and medulla. Focal hemorrhages and much perivascular cuffing of lymphocytes were present.

Bone Marrow: There was a great predominance of lymphocytes and a definite suppression of red blood cells. No megakaryocytes were seen. Phagocytes containing hemosiderin were prominent.

Brain: Massive hemorrhage was seen, as well as lymphocytic infiltration beneath the dura. Large deposits of golden brown pigment were visible.

The final anatomic diagnosis was: chronic lymphoid leukemia with generalized lymphadenopathy, splenomegaly, hepatomegaly and renal enlargement; multiple pulmonary hemorrhages; bronchopneumonia; petechiae of skin, oral mucosa, pericardium, pleura and bladder mucosa; perirenal and intrarenal hemorrhage; subdural hematoma with leukemic infiltration; subarachnoid hemorrhage; cardiac hypertrophy; drainage and surgical incision in medial portion of left thigh, and hemosiderosis of liver, spleen and bone marrow.

COMMENT

The first definite diagnosis in this case was made from a sternal biopsy specimen. The efficacy of this method of obtaining a diagnosis was emphasized by Vogel and Bassen [4] in 1939. Although the only symptoms observed early in the course of the disease in this patient were those associated with obscure anemia, nevertheless other classic signs of acute leukemia, such as thrombopenia, bleeding tendencies, enlargement of the spleen and liver and changes in the peripheral blood eventually made their appearance and made the diagnosis obvious. The eventual appearance of these classic signs in our patient causes us to consider her disease as one of the general group of acute leukemias rather than as an example of the more chronic type usually observed in adults.

The patient lived twenty months after the onset of the disease and eighteen months after the diagnosis had been suggested by sternal biopsy specimen. It cannot be denied that the vigorous supportive treatment, including transfusion, high voltage roentgen therapy and administration of "aminopterin," was partially responsible for the prolonged course.

A review of the literature indicates that case reports of leukemia in children with prolonged survival periods are not entirely satisfactory. In some instances the disease is designated as myeloid leukemia; in others there is inadequate information. In 1927, Ramsay [2b] analyzed 100 cases from the medical literature up to that time, including 9 cases which he personally observed in Glasgow, Scotland, and found the average duration in lymphoid and lymphoidocytic leukemia to be two months. The longest survival he recorded was in a child with myelogenous leukemia who lived two years after the apparent onset of the disease.

In 1932, in a report of 28 cases from the Babies Hospital in New York, Wollstein [5] stated that the longest survival was six months.

In 1933, Cooke [1] reported 15 cases. The longest survival of children with the acute disease was nine months. There were 3 patients with chronic myelogenous leukemia of whom 1 was still alive at the time of the report, and the other 2 died at fourteen months and two years, respectively, after onset.

In 1937, Abt [2c] stated that chronic lymphoid leukemia did occur in children but was extremely rare. The longest survival he reported was two years in a child with myelogenous leukemia.

In 1938, Spigel [6] discussed several cases which he designated as of the "acute" and "chronic" types, but his diagnostic criteria did not appear to be well defined.

In 1938, Simonson [2e] reported 16 cases, in which the longest survival was eight and a half months.

4. Vogel, P., and Bassen, F. A.: Sternal Marrow of Children in Normal and Pathologic States, Am. J. Dis. Child. **57**:245 (Feb.) 1939.

5. Wollstein, M.: Leukemia in Young Children, Am. J. Dis. Child. **44**:661 (Sept.) 1932.

6. Spigel, H. A.: Leukemias of Infancy, Arch. Pediat. **55**:332, 1938.

In 1939, Craver [5d] described 10 cases of leukemia lasting from eight days to two years but failed to report the one with the two year survival in detail.

In 1943, Falkenstein and Fowler [5b] reported 61 cases from the Iowa University Hospital in which the longest survival was fourteen months.

In 1944, Haltman [7] recorded a single case which resembled our case symptomatically. In his case, however, survival was only eight months.

The most recent report is that of Dale [5i] of 72 cases from the New York Hospital, in which the longest survival was two years ten months. It is not stated whether this case was of the lymphoid or the myeloid type, nor does the author indicate whether or not the diagnosis was confirmed by autopsy observations.

It is only fair to admit that the case reported is not of the longest survival in a child with leukemia recorded in the medical literature. Nevertheless, this case presents certain points that, in our opinion, justify a report of it. The diagnosis of lymphoid leukemia is clearly established by the clinical and laboratory data and by the pathologic findings. It is one of the few cases of authenticated survival in a child with lymphoid leukemia beyond eighteen months. Finally, the presentation of such a case in detail may aid in the further simplification of the classification of leukemias in childhood. It seems that the simplest classification is that of Cooke,[1] which lists the disease as chronic myelogenous leukemia and acute leukemia, with the term chronic lymphoid leukemia reserved for the well recognized adult disease.

SUMMARY

A case of acute lymphoid leukemia in an infant of the unusually long survival period of twenty months is presented in detail. Reports of the duration of childhood leukemia in the literature are reviewed. The simpler classification of childhood leukemias suggested by Cooke is recommended.

1039 Wall Street (Dr. Moody).

7. Haltman, S. T.: Case of Atypical Acute Leukemia, Nord. med. **21**:15, 1944.

EPENDYMOMA OF LATERAL VENTRICLE

Report of a Case of More Than Twelve Years' Survival

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The cloud of pessimism about intracranial neoplasms in children has been lifting slowly during the past two decades. In 1927, Cushing [1] sounded an optimistic note when he reported on 6 patients with ependymoma in a series of 116 intracranial neoplasms in children below 15 years of age. These 6 patients had an average survival period of over twenty-five months. Ten years later, Eisenhardt [2] included in her report of long postoperative survivals after intracranial tumors a child 10 years of age from whom an ependymoma of the fourth ventricle was removed. The child was living and well thirteen years after the operation. Although gliomas in children in either cerebral hemisphere are often malignant, the ependymomas offer the best prognosis. These tumors, though infrequent, have some clinical features in common and may even be completely enucleated with a permanent cure.

Of the 8 patients with ependymomas reported on by Fincher and Coon [3] in 1929, 5 were under 12 years of age, the youngest being 16 months of age. She had a parietofrontal ependymoma on the right weighing 270 Gm. Five of these ependymomas were in either cerebral hemisphere, of which 3 showed calcification on roentgenogram.

In Cushing's report in 1932 [4] of a series of 2,000 verified intracranial tumors 25 were ependymomas. Nine were in the cerebellar region and only 6 were found in the cerebral hemispheres and apparently had their origin from the ependymal cells lining the ventricles. There were 2 operative fatalities.

In the study of 109 patients with ependymomas from the Mayo Clinic by Kernohan and Fletcher-Kernohan [5] in 1937, 55 growths were in the spinal canal and 54 in the intracranial cavity. Of these, 6 had their origin in the right ventricle and 7 in the left ventricle. The authors reported only a small group of these ependymomas to be extremely malignant. Four patients in their series were still alive fifteen years after operation.

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1. Cushing, H.: Intracranial Tumors of Preadolescence, Am. J. Dis. Child. **33**:551 (April) 1927.

2. Eisenhardt, L.: Long Postoperative Survivals in Cases of Intracranial Tumor: Tumors of the Nervous System—An Investigation of the Most Recent Advances, A. Research Nerv. & Ment. Dis., Proc. (1935) **16**:390, 1937.

3. Fincher, E. F., Jr., and Coon, G. P.: Ependymomas: A Clinical and Pathologic Study of Eight Cases, Arch. Neurol. & Psychiat. **22**:19 (July) 1929.

4. Cushing, H.: Intracranial Tumors: Notes upon a Series of 2,000 Verified Cases with Surgical-Mortality Percentages Pertaining Thereto, Springfield, Ill., Charles C Thomas, Publisher, 1932.

5. Kernohan, J. W., and Fletcher-Kernohan, E. M.: Ependymomas: A Study of 109 Cases, A. Research Nerv. & Ment. Dis., Proc. (1935) **16**:182, 1937.

The following case is reported because this patient is the youngest on record to have a complete removal of an ependymoma from the lateral ventricle, because so few and contradictory clinical findings were produced by so large a neoplasm, because of the interesting ventricular studies and because of the patient's continued survival period in excellent health in spite of malignant histologic findings.

REPORT OF CASE

On the evening of Nov. 10, 1937, Dr. Joseph A. Trackman, New York, was called to treat an elderly woman for an infection of the upper respiratory tract. On entering the home, he spotted her young grandson, aged 5, with a large head and dilated venules over the forehead. This prompted him to percuss the skull, and he elicited a "cracked-pot" sound (Macewen's sign). He looked into the boy's fundi, found bilateral papilledema with secondary optic atrophy and immediately arranged for his admission to the hospital.

On the following day the parents gave the following account of their son's illness. He was their first-born child, was delivered normally and had developed like other children of his age. Mentally he was perhaps a little brighter than some of his playmates. He had had no unusual illness or trauma. He appeared well and healthy until ten months before his admission, when he began to complain of some generalized headaches. Slowly the headaches increased in frequency and severity and for six months they were chiefly referred to the suboccipital region.

The suboccipital headaches were associated with matutinal vomiting. Though he liked school and was considered a bright pupil, the vomiting was interpreted as an excuse to stay home from school. Yawning and nose rubbing were noted for several months before his admission. The large head and dilated veins over the forehead were observed without any special concern. For two months before his admission the gait became increasingly unsteady. For diminution of vision glasses were obtained. It could not be determined whether the boy bumped into objects on either side.

Examination showed the following positive findings: The boy was alert, bright and cheerful, with no special complaints. The head was large and the scalp veins were strikingly prominent. A definite Macewen sign was readily elicited. Vision was reduced to perception of gross finger movements. The pupils were dilated, and the fundi showed advanced bilateral papilledema with secondary optic atrophy. There was some horizontal nystagmus to the left. The gait was broad based, and the extremities showed hypotonia. The finger to nose test was performed with slight ataxia on the right. The deep reflexes were sluggish, but there were no pathologic toe signs.

Results of urinalysis were normal. The hemoglobin concentration was 11.5 Gm.; the red blood cells numbered 3,840,000 and the white blood cells 15,150, with 63 polymorphonuclear leukocytes, 34 lymphocytes and 1 mononuclear cell. The Kahn reaction was negative. The presence of a cerebellar neoplasm was suspected.

On November 13, with the boy under local anesthesia induced with procaine hydrochloride (novocain®) a skull trephinement was performed on the right. Sixty cubic centimeters of clear, colorless fluid was obtained from the right ventricle and 40 cc. of air was injected. Roentgenograms of the skull showed a dilated right lateral ventricle which was not displaced, but no air passed into the third or left lateral ventricle. The patient was returned to the operating room and a skull trephinement was made on the left side. Only 10 cc. of clear fluid was obtained and an equal quantity of air was injected. Roentgenograms of the skull revealed

a compressed left lateral ventricle with a smooth crescentic defect in the left occipital region displacing the occipital horn downward and also showed some air above the displacing mass. (figs. 1 and 2). Immediate operation had to be postponed

Fig. 1.—Air in both ventricles showing compression of left ventricle and displacement to the right.

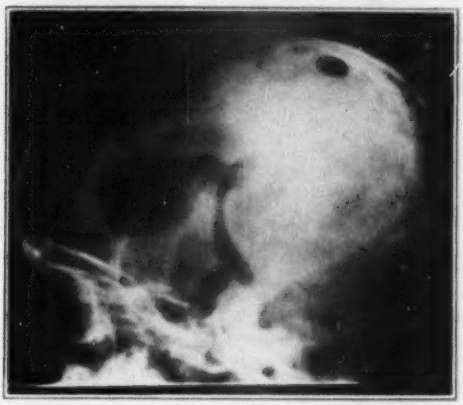

Fig. 2.—Lateral view showing forward compression of left lateral ventricle with curved shadow marking the anterior margin of the neoplasm.

because the patient's parents on their way to the hospital that morning were in an automobile accident.

Operation (November 16).—As the area for craniotomy was outlined in the left parieto-occipital region with the use of local procaine anesthesia, the patient

began to show signs of decerebrate rigidity. Hypertonic dextrose solution was given intravenously immediately and the operation was continued with reasonable haste. The decerebrate phenomena wore off after several minutes. When the dura was exposed, it appeared normal in color but failed to pulsate. The dura was incised in a curved fashion and reflected toward the midline. The cerebral cortex showed only flattened convolutions. An incision was, therefore, made through the cortex in the postparietal region, and at a depth of 0.5 cm. a reddish brown, well demarcated neoplasm came into view. A small portion was removed with an electric loop

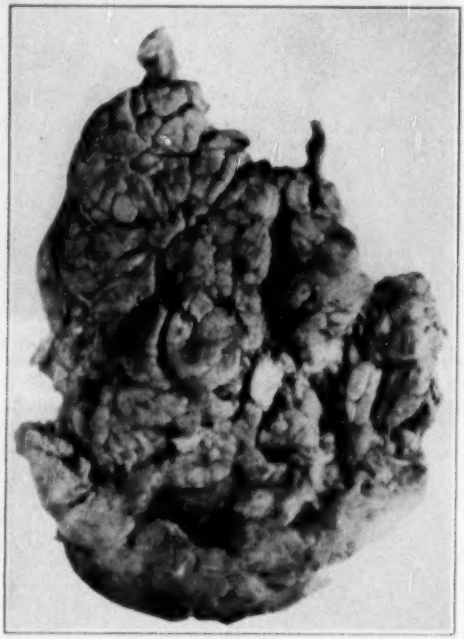

Fig. 3.—Superior surface of neoplasm, measuring 12 by 16 cm.

for microscopic study. As this study was in process the brain began to swell and at a great risk it was decided to remove the entire growth. It was observed to extend into the lateral ventricle. Because it was well demarcated it was removed in one piece. As the tumor was tilted out of the lateral ventricle, there was some brisk bleeding which soon was brought under control. The patient's blood pressure and pulse in the meantime became imperceptible; he appeared ashen gray but respirations continued in a slow and deep manner. The blood transfusion which had already been started was speeded up. Fifteen minutes after the removal of the tumor an occasional pulse beat could barely be felt at the wrist. A few minutes later a blood pressure reading was obtained. Steadily the pulse rate and blood

pressure returned to more comfortable readings. The ependymal lining of the left ventricle was thoroughly inspected, and there were no remains of neoplasm. After all the bleeding was controlled, the wound was closed in layers. By the time the dressing was applied the patient had regained consciousness and the pulse rate and blood pressure were satisfactory. The tumor weighed 191.5 Gm. (fig. 3).

Course in Hospital.—During the first fortnight following the operation the patient had a moderate elevation in temperature, at times rising to 103 F., but there were no headaches or vomiting, and he remained cheerful and mentally alert. Some fluid accumulated under the bone flap, but this required only two aspirations. Roentgenologic studies of the chest showed no lesions, and blood studies gave normal results. From then on the daily improvement was gratifying. The papilledema receded completely; the nystagmus disappeared; the dilated venules over the forehead became invisible, and the Macewen sign could no longer be elicited. Except for residual secondary optic atrophy, there were no abnormal neurolgic signs. Vision, which before the operation was reduced to perception of gross finger movements, also improved, so that on December 8, twenty-six days after the operation, the date of his discharge from the hospital, he could recognize faces and outlines of familiar objects (fig. 4).

Fig. 4.—Postoperative view showing normal contour of head.

Microscopic study of this tumor (by Dr. Louise Eisenhardt, from the Brain Tumor Registry) showed that it was peculiar histologically in that it had a wind-

blown appearance, with widely scattered clusters of cells in a relatively abundant fibrillary substance; yet the tumor appeared to be rapidly growing. The most suggestive architecture on the whole was that of an ependymal tumor with cells arranged at the periphery of perivascular fibrillary substance. The cells had a small roundish nucleus and, in general, showed a poorly defined scanty cytoplasm, though tailed forms were present. Mitotic figures were present and in some areas the blood vessels showed endothelial proliferation (fig. 5).

The diagnosis was ependymoblastoma. Roentgen therapy was not given.

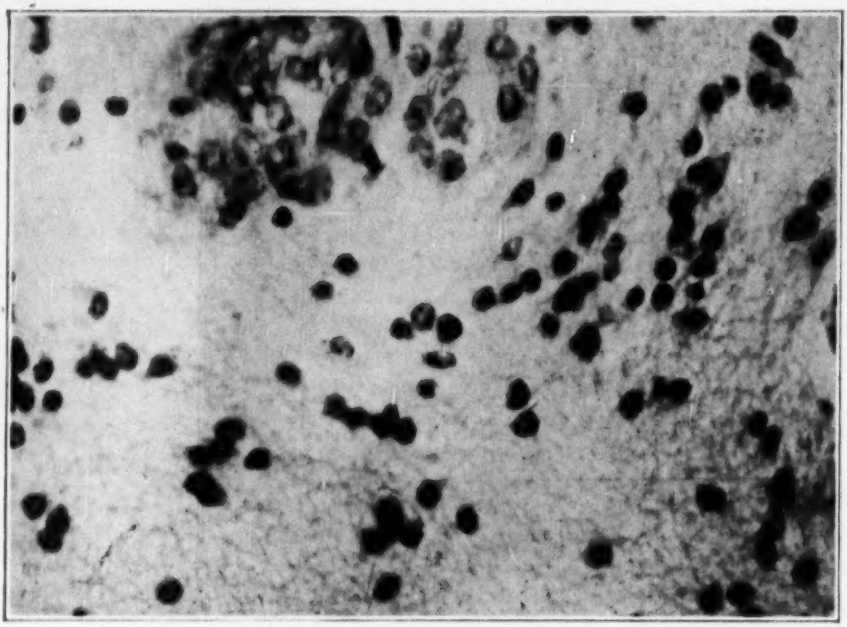

Fig. 5.—High power view showing small roundish nuclei with mitotic figures and endothelial proliferation.

Further Observations.—Since his discharge from the hospital, almost twelve years ago, this boy has hardly had a sick day. A brief summary of his accomplishments may be quoted from a recent letter, dated Oct. 22, 1949.

"I graduated from elementary school in 1945 and was awarded the Gold Medal for English.

"My next four years were spent in Fordham Preparatory School from which I graduated in June 1949, with an average of 81 per cent. While attending Fordham, I was a member of the Debating Society, Radio Club, History Club, Sodality, K.B.S., Sanctuary Society and Auxilium Latinum, and wrote for the Rampart, the

semimonthly school paper, conducting a column for four years. On graduating I was awarded a Key for outstanding work on the school paper.

"I am now attending the New York State Agricultural and Technical Institute in Delhi, N. Y. I am majoring in animal husbandry with dairy industry as my minor. This course also consists of botany, poultry husbandry, farm mechanics, bacteriology, chemistry, physics, and farm marketing. There is also a course in psychology.

"I will attend this college for two years and hope to finish my education at Cornell University for my B.S. degree.

"It is necessary for me to wear special glasses for reading and with these glasses I can read the smallest print."

30 East Fortieth Street (16).

MULTIPLE SUBDURAL HEMATOMAS IN AN INFANT

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According to the work of Gardner,[1] Leary,[2] Voris[3] and others, the source of hemorrhage in subdural hematoma of the chronic variety is usually at the point where the central veins enter the longitudinal sinus. Blows in the anteroposterior plane are prone to produce a shearing effect on these vessels, rending them from their insertion in the sinus and permitting the escape of venous blood into the subdural space. While this explanation holds good for the vast majority of adult subdural hematomas, it is somewhat less valid as the cause of the infantile subdural hematoma.

Sherwood[4] first called attention to the clinical symptoms and findings of subdural hematoma in infants and reported 9 cases with only 1 death. He considered the causation "obscure." Ingraham and Matson,[5] in one of the finest presentations on subdural hematomas in infancy yet published, discussed the pathologic aspects of the lesion in children. They emphasized the importance of trauma (frequently "trivial") in the production of subdural hematomas and were somewhat disinclined to regard blood dyscrasias as a significant contributor to the pathogenesis. Thrombosis of dural sinuses, believed to be an important factor in the case herein presented, was not mentioned by them.

The molding of the head as it passes through the birth canal is a well known fact. When biparietal pressure is exerted on the cranium, there is a tendency for the brain itself to be displaced downward. Since the longitudinal sinus is supported by the upper margins of the parietal bones, it cannot ordinarily accompany the brain when this displacement occurs. Consequently, the central veins will be stretched and may rupture.

In the case here presented of multiple subdural hematomas, the observations tend to illuminate still another mechanism in the formation of subdural clots.

REPORT OF A CASE

History.—This male white child was born Jan. 24, 1948, in Cleveland. Notes from the institution in which he was born indicated that he was a full term

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From the Departments of Neurosurgery of George Washington University and The Children's Hospital.

1. Gardner, W. J.: Traumatic Subdural Hematoma with Particular Reference to Latent Interval, Arch. Neurol. & Psychiat. **27**:847-858 (April) 1932.

2. Leary, T.: Subdural or Intradural Hemorrhages, Arch. Path. **28**:808-820 (Dec.) 1939.

3. Voris, H. C.: Subdural Hematoma, J. A. M. A. **132**:686-692 (Nov. 23) 1946.

4. Sherwood, D.: Chronic Subdural Hematoma in Infants, Am. J. Dis. Child. **39**:980-1021 (May) 1930.

5. Ingraham, F. D., and Matson, D. D.: Subdural Hematoma in Infancy, J. Pediat. **24**:1-37 (Jan.) 1944; correction, **24**:221 (Feb.) 1944.

baby. Labor totalled five hours, and he was delivered by low forceps with episiotomy. Respirations were spontaneous and prompt and no resuscitative measures were indicated. The weight at birth was 7 pounds 3 ounces (3,260 Gm.). He was discharged from the hospital one month later with a weight of 8 pounds 3 ounces (3,714 Gm.), and during the stay in the hospital no abnormalities were noted. At the time of discharge the fontanels were small and soft, the eyes and extremities normal and vision apparently normal. On April 24 the patient was examined by Dr. C. T. J. Dodge, of East Cleveland, Ohio, who found the weight to be 12 pounds (5,443 Gm.). The circumference of the head was 43 cm. and of the chest 38 cm. On June 25 the patient's weight was 15½ pounds (7,031 Gm.); the circumference of the head had increased to 47 cm. and that of the chest to 41 cm. A further note stated that the fontanel was large and quite tense; the eyes turned downward; the general physical condition was good, and the mentality appeared to be about normal. It was recommended that he be admitted to a hospital for further investigation with the tentative diagnosis of subdural hematoma. No history whatsoever of any injury was obtained. On July 9 he was seen in the Neurological Clinic of The Children's Hospital of Washington, D. C., where the measurements were approximately the same as those noted by Dr. Dodge; the child seemed alert but did not sit up. The ocular fundi were normal, and the anterior fontanel was 5 by 5 cm. but not tense. The reflexes of the upper extremities were depressed, but those of the lower extremities were brisk and the muscles spastic.

Course in Hospital.—The child was admitted to the hospital. A roentgenographic examination of the skull revealed it to be enlarged in all diameters, but without abnormal separation of the sutures. On July 13 a bilateral subdural tap was performed which resulted on the right in the recovery of a moderately large amount of fresh blood mixed with a little spinal fluid. This mixture did not clot. The needle was advanced to a depth of 3 cm. and no ventricle was encountered. On the left, subdural tap also revealed some fresh bleeding but in a smaller amount, and, on advancing the needle to a depth of 3 cm., some xanthochromic fluid was recovered. No clotting in any specimens occurred after twelve hours, and the supernatant fluid in all specimens was xanthochromic.

Pediatric consultation was requested to determine the possibility of a blood dyscrasia. The bleeding time was found to be seventy-five seconds and the coagulation time four minutes. The hemoglobin concentration was 11 Gm.; the red blood cells numbered 3,600,000 and the white blood cells 9,200, with 79 per cent neutrophils, 7 per cent small lymphocytes and 200,000 thrombocytes. A moderate anisocytosis with microcytosis was present. No clinical evidence of scurvy was found. The blood vitamin C level was 0.5 mg. per hundred cubic centimeters (normal, 0.7 to 1.5 mg.). When bilateral subdural taps were repeated, a small amount of deeply xanthochromic fluid was recovered on the right. The right ventricle was not located, but on the left some xanthochromic spinal fluid was obtained as in the previous tap. Four days later the child was taken to the operating room and bilateral burr holes were made in the frontoparietal region approximately over the coronal sutures. On incision of the dura on the left there was a gush of what appeared to be fresh venous blood. It was observed, however, that this fluid was not of the normal viscosity of blood. After approximately 45 cc. had escaped, it was possible to observe the internal limits of this cavity. Here a greenish gray fibrinous-looking membrane was seen, and the brain could not be visualized through it. This membrane was incised and stripped back, permitting another gush of fluid to appear. This fluid, however, was somewhat darker in appearance than the first, i. e., an older hematoma. After this cavity was irrigated, again there was

observed a dense opaque membrane obscuring the brain. The second membrane was ruptured, permitting the escape of a third hematoma containing dark chocolate fluid.

It was now possible to visualize the cerebral cortex lying underneath a ballooned arachnoidal membrane. The cortex itself lay approximately 3 cm. below the inner surface of the skull. It appeared to be of normal color and vascularity, though the convolutions were a little narrow and the sulci correspondingly widened.

On the right side a similar procedure was carried out with identical results except that four subdural hematomas of apparently increasing age were encountered before the cortex was visualized. Portions of the membranes were taken for pathologic study. The brain appeared normal except that it was considerably smaller in all visible dimensions than the size of the head would have led one to believe. The hematomas extended from the frontal pole to the posterior pole bilaterally.

Penrose drains were inserted through each burr hole and into the subdural space and led out through the skin incisions, which were closed with black silk sutures.

The microscopic report on the tissue removed was as follows: "One border is made up largely of fibrous tissue in which there are a number of vascular spaces and some collections of blood and blood pigment. Internal to this is a loose fibrinous membrane."

Two days after the operation abundant clear drainage had occurred and both drains were removed.

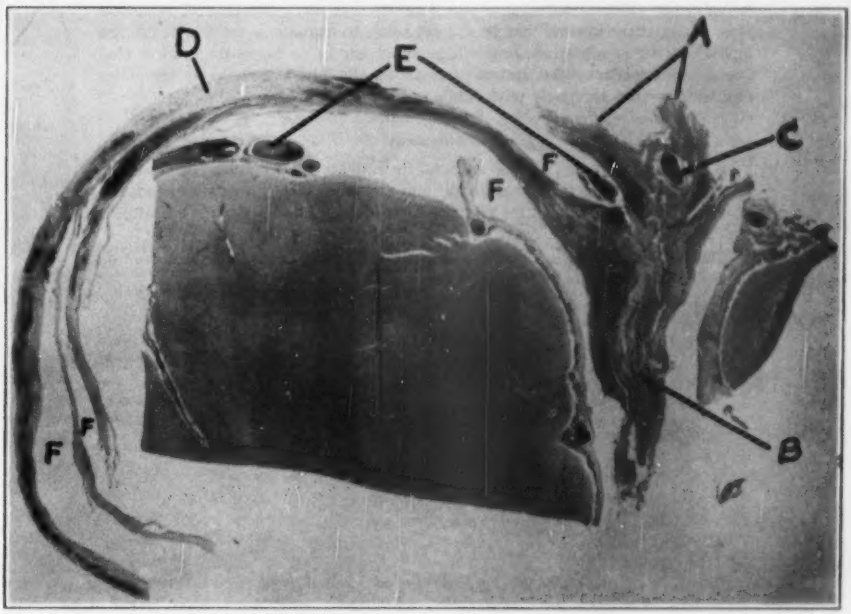
One week postoperatively, the burr holes were bulging and 10 to 15 cc. of xanthochromic fluid was removed through each burr hole. The child's condition was excellent and there was no postoperative elevation in temperature. Three days later more fluid was aspirated, followed by about 8 to 10 cc. of bright red blood. The reaccumulation of this fluid had opened the wound margins so that a fistula was established. It was apparent that more hemorrhage had occurred. The child was given penicillin and sulfadiazine in an effort to thwart the development of meningitis. The temperature still remained normal. Two weeks postoperatively, the patient suddenly became pallid and cyanotic and convulsive twitches developed, with coldness of extremities noted. A grunting respiration appeared and some rales were detected in the base of the right lung anteriorly. A few minutes later the patient died.

Autopsy Observations.—Autopsy was performed seven hours later (Dr. E. Clarence Rice). Except for some congestion of the lungs, spleen and adrenal glands, the major observations were in the cranium. Both transverse sinuses, the occipital sinus and the right superior petrosal sinus were completely thrombosed with organization.

No brain tissue was visualized after turning back four large bone flaps. Instead, the cerebral hemispheres were covered with a thick, yellowish, membranous structure which had flattened the frontal and parietal lobes bilaterally. This membranous structure had been entered on both sides beneath the sites of the burr holes, and several extensive walled-off cavities were recognized on each side representing bilateral hematoma (figure). The cavity on the left contained a small amount of yellowish exudate. None of the spaces contained blood or bloody fluid. After fixation in solution of formaldehyde U. S. P. the membranes of the hematoma could be separated into several layers. The convolutions were compressed and the cerebral vessels were engorged. A cortical vein on the left coursed up through the several layers, where a small fresh area of clot could be seen close to the

longitudinal sinus. Coronal section showed no abnormality except for some cerebral vessels which were thrombosed. The longitudinal sinus was likewise thrombosed but recanalized. Thrombosis of the lateral sinus was also observed.

Histopathologic Report: The pia-arachnoid showed a number of fibroblasts and fibrocytes in which were intermingled numerous leukocytes, principally polymorphonuclear forms. The arachnoidal vessels were engorged. Adjacent brain tissue revealed a slight invasion by leukocytes with prominent filling of the capillaries with erythrocytes. Some gliosis was evident. Above the pia-arachnoid were several coverings of connective tissue which were well vascularized and invaded by leukocytes.



Photomicrograph showing (*A*) dura, (*B*) falx, (*C*) longitudinal sinus (thrombosed and recanalized), (*D*) neomembrane, (*E*) cortical vein, revealing that the probable site of the latest hemorrhage, as well as that of the previous hemorrhages, was near the falx and (*F*) four cavities containing hematomas observed at operation.

COMMENT

It appears on the review of the operative and the autopsy observations that this child had repeated subdural hematomas, each one apparently independent in time of the other. Those encapsulated hematomas most closely applied to the brain were the oldest, while progressively more recent hemorrhages, if judged by the color of the fluid, lay nearer the skull. The vessel probably responsible for the hemorrhage on the left was later identified as one of the central veins. The vessel on the right presumed to be responsible was not clearly identified.

The extensive thromboses of the dural sinuses probably contributed to the repeated hemorrhages by the increased intrasinus pressure caused by their presence. These thromboses undoubtedly had their origin as marantic thrombi induced in the longitudinal sinus following the first hemorrhage that had gradually filled most of the dural sinuses over the convexity. In such circumstances the venous pressure within the cortical veins was bound to rise and this plus a trivial jar was sufficient to "blow out" the scarred and weakened junction of the vein and the sinus. The dense and extensive membranes as observed at autopsy could be stripped one from another (and from the brain) over the complete extent of the convexity of the brain. They did not communicate as do loculated hematomas.

It is of interest that this case clearly reveals the commonest origin of the formation of subdural hematomas and suggests that the appearance of symptoms after a long latent interval may be due not solely to increase in the size of the clot by osmosis but to subsequent hemorrhage either into or on top of the original clot. Sinus thromboses may abet such a process. Finally, late appearance of symptoms can result from a seemingly trivial injury.

SUMMARY

A case of bilateral multiple subdural hematomas in an infant is described. It is believed that this case gives insight into a mechanism of formation of subdural hematomas and may explain the ultimate appearance of clinical signs in hematomas with long latent intervals.

The existence of three separate subdural hematomas on one side and four on the other is recorded because of its rarity.

2014 R Street, N. W. (9)

ADDISON'S DISEASE IN A FIVE AND ONE-HALF YEAR OLD BOY

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AND
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Chronic adrenal insufficiency (Addison's disease) is extremely rare in the pediatric age group. In the approximately 100 such cases that have appeared in the literature to date, less than one fourth of the patients were children under 10 years of age.[1] Adrenocortical tuberculosis was etiologically responsible for the majority of cases, whereas a smaller percentage was ascribed to bilateral adrenal cortex atrophy, agenesis or degeneration of unknown origin and hyperplasia of the adrenogenic zone of the cortex. Other etiologic factors responsible for the destruction of the adrenal cortex and the syndrome of Addison's disease in adults, namely, pyogenic abscesses, vascular lesions, mycosis fungoides, echinococcic cysts, amyloidosis, neoplasms, histoplasmosis, moniliasis and diphtheria, have not been demonstrated in children.[2]

Because of the relative rarity of Addison's disease in infancy and early childhood, the following case of the disease due to bilateral adrenal cortex atrophy in a 5½ year old boy was considered worthy of recording.

REPORT OF A CASE

First Admission.—F. O., a 5 year 10 month old white boy, was first admitted to Children's Hospital on Oct. 10, 1947 in a comatose state. He had apparently been perfectly well until four months previously, when he began losing his original zest for physical activities. Frequent episodes of evening and early morning emesis occurred during that time. He consumed such large quantities of water that his abdomen was frequently distended. Nocturnal and diurnal urinary frequency, a

From the Departments of Medicine and Pathology, Children's Hospital.

1. (*a*) Anderson, J. A.: Significance of Adrenal Insufficiency in Childhood, Journal-Lancet **62**:161 (May) 1942. (*b*) Davison, W. C.: The Compleat Pediatrician, ed. 6, Durham, N. C., Duke University Press, 1949, p. 140. (*c*) Talbot, N. B., in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Co., Inc., 1948, vol. 1, chap. 40, p. 22. (*d*) Chenoweth, B. M., Jr.: Dysfunction of the Adrenal Gland in Infancy, South. M. J. **41**:307 (April) 1948. (*e*) Addison, T.: Anemia: Disease of the Suprarenal Capsules, London M. Gaz. **43**:517, 1849. (*f*) Jaudon, J. C.: Addison's Disease in Children, J. Pediat. **28**:737 (June) 1946. (*g*) Wilkins, L.; Fleischmann, W., and Howard, J. E.: Macrogenitosomia Praecox Associated with Hyperplasia of the Androgenic Tissue of the Adrenal and Death from Corticoadrenal Insufficiency: Case Report, Endocrinology **26**:385 (March) 1940.

2. Davison,[1b] Jaudon,[1f] Conn, J. W., and Mathews, K. P.: Addison's Disease in the Negro, Am. J. M. Sc. **212**:404 (Oct.) 1946.

gradually progressive weight loss and an excessive craving for large quantities of table salt on all foods (including bacon) were prominent features. Because of extreme weakness, he would occasionally take "naps" lasting all morning and would participate only in sedentary activities. He was described as having always been a "nervous" child, who manifested occasional temper tantrums and frequently wet the bed.

During the twenty-seven hours prior to admission he vomited several times, became restless and weak, consumed only three small glasses of ice water and tea and passed seven large watery green stools. He slept restlessly most of the time until three hours before admission, when he had a temperature of 103 F., vomited profusely and lapsed into a state of deep coma.

The past medical history disclosed that he had pertussis at 2 years of age, "mild" pneumonia at 3 years, chickenpox at 5 years and an occasional "cold." All illnesses were uncomplicated. He was born uneventfully after a full term pregnancy, and his physical and mental growth and development had been within normal limits until the onset of the present illness. The family history was noncontributory.

Physical examination on admission disclosed a fairly well developed, pale, dehydrated, deeply comatose boy. The respirations were rapid; the pulse rate was 110 per minute, and the blood pressure 85 systolic and 30 diastolic. The eyes were sunken; the abdomen, soft and flat, and poor tissue turgor was evident. The spleen was palpable 2 fingerbreadths below the left costal margin. Feeble withdrawal of the extremities was the only response to pinprick. All deep tendon reflexes were hypoactive and equal bilaterally. Frequent bouts of tonic spasms of the arms and legs accompanied with aimless wandering of the eyes occurred intermittently for approximately six hours after hospitalization. The rest of the physical examination revealed no other abnormalities.

The results of laboratory examinations were as follows: The blood sugar on admission after intravenous injection of sodium lactate was 83 mg. per hundred cubic centimeters; the spinal fluid on admission was normal except that it contained 10 mg. of sugar per hundred cubic centimeters; two other determinations showed 35 and 40 mg. of sugar per hundred cubic centimeters. The urine and the complete blood count were within normal limits on two occasions; the reaction to an intradermal test with old tuberculin was negative. It seemed likely that the blood sugar level of 83 mg. per hundred cubic centimeters obtained shortly after admission was considerably lower prior to the intravenous administration of sodium lactate, since the spinal fluid sugar level determined shortly after the infusion was only 10 mg. per hundred cubic centimeters. A rise in the blood sugar level is not infrequently encountered after procedures that tend to produce physiologic epinephrine responses.

The patient was treated for the apparent dehydration, acidosis and hypoglycemia existing at the time of admission with intravenous administrations of sodium lactate and 5 per cent dextrose in isotonic sodium chloride solution, with slow steady recovery. Within twelve hours of the initiation of therapy the temperature was normal; the patient yawned frequently, sat up jittery and feeble, focused his eyes on his surroundings, conversed and seemed oriented as to place and person. During the remaining six days of hospitalization, he complained of an occasional vague pain in the upper part of the abdomen and a mild frontal headache. The diarrhea persisted for three days, responding to symptomatic treatment. At the time of discharge, on October 17, he was mentally alert and had recovered sufficiently to engage in sedentary and mildly active play, although he required long morning

and afternoon rest periods. His blood pressure was 85 systolic and 45 diastolic. The diagnosis at that time was "idiopathic hypoglycemia," and home management was directed on that basis.

Second Admission.—On December 9, approximately eight weeks after discharge, the patient was again admitted, because of coma of three hours' duration. During the previous two weeks his lethargy and weakness following exercise had become more pronounced, so much so that he preferred only sedentary play. He was annoyed by occasional attacks of transient vague pains in the upper part of the abdomen and an occasional vomiting spell. His appetite was fair until twenty-four hours before admission, when he vomited several times and lapsed into a light sleep, from which he was easily aroused. This progressed to a state of deep coma which was soon complicated by transient generalized convulsions.

Physical examination at the time of admission disclosed conditions somewhat similar to those elicited on his first hospitalization; namely, moderate dehydration, aimless wandering of the eyes, pallor, regular respirations, flaccid extremities, hypoactive and bilaterally equal deep tendon reflexes, weak response to sensory stimuli, coma and a blood pressure of 80 systolic and 40 diastolic. The temperature was subnormal (96.4 F.) rather than elevated as previously. In addition, about twenty small flat black pigmented areas measuring up to 2 mm. in diameter were noted for the first time on the skin of the face and the anterior and posterior parts of the trunk.

Approximately two hours after receiving sodium lactate and 10 per cent dextrose solutions intravenously, he appeared alert and well oriented; however, shortly thereafter he again lapsed into a state of coma and again responded to similar intravenous injections of fluids. During the rest of the hospital stay he preferred sedentary play to more strenuous activities. His daily blood pressure varied from a low of 86 systolic and 36 diastolic to a high of 100 systolic and 60 diastolic.

The results of laboratory examinations were as follows: On admission the carbon dioxide-combining power was 20 volumes per cent and twenty-four hours later 48 volumes per cent; the admission blood sugar level was 37 mg. per hundred cubic centimeters, eight daily fasting blood sugar levels ranged from 47 to 100 mg. per hundred cubic centimeters with an average of 69 mg.; five blood sugar levels obtained three to four hours after a carbohydrate meal ranged from 47 to 222 mg. with an average of 143 mg. per hundred cubic centimeters; results of two urinalyses and one spinal fluid examination were essentially normal, with a spinal fluid sugar level of 35 mg.; serum plasma chloride as sodium chloride was 790, 540 and 502 mg. per hundred cubic centimeters; serum sodium level was 116 milliequivalents per liter; the cephalin flocculation reaction was 2 plus in forty-eight hours, and serologic tests for syphilis elicited negative reactions. A roentgenogram of the skull and a flat plate of the abdomen disclosed no abnormalities.

Laboratory, roentgenologic and clinical findings seemed to eliminate the possibility of hepatic, pituitary or central nervous system lesions.

The diagnosis of chronic adrenal cortex insufficiency was contemplated in view of the patient's progressive weakness, hypotension, skin pigmentation, hypoglycemic crises, abnormal craving for table salt, gastrointestinal symptoms and low blood chloride and low serum sodium levels. Therefore, from the third through the seventh day, he received daily 2 cc. of adrenal cortex extract intramuscularly and 3 Gm. of enteric-coated sodium chloride orally. This regimen apparently failed to produce any noticeable change in his behavior or well-being; hence it was discontinued. Admittedly, the dosage of adrenal cortex extract employed was entirely inadequate; however, owing to a misunderstanding, adequate hormonal therapy was never achieved.

Fig. 1.—Small generalized black pigmented skin lesions.

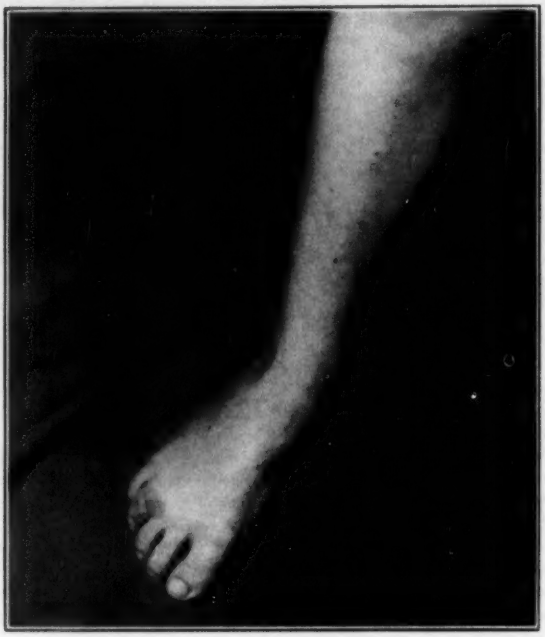

Fig. 2.—Café au lait lesion on the dorsum of the right third and fourth toes.

On the nineteenth day about twenty additional generalized black-pigmented areas were noted on the skin, as were two café au lait spots in the left inguinal fold measuring 1.5 and 3.0 cm. in diameter respectively and a café au lait lesion on the dorsum of the right foot, at and extending onto the base of the third and fourth toes, measuring 1.5 cm. in diameter. Figures 1 and 2 show clearly the generalized tiny black-pigmented spots and the café au lait lesion on the right foot. Several

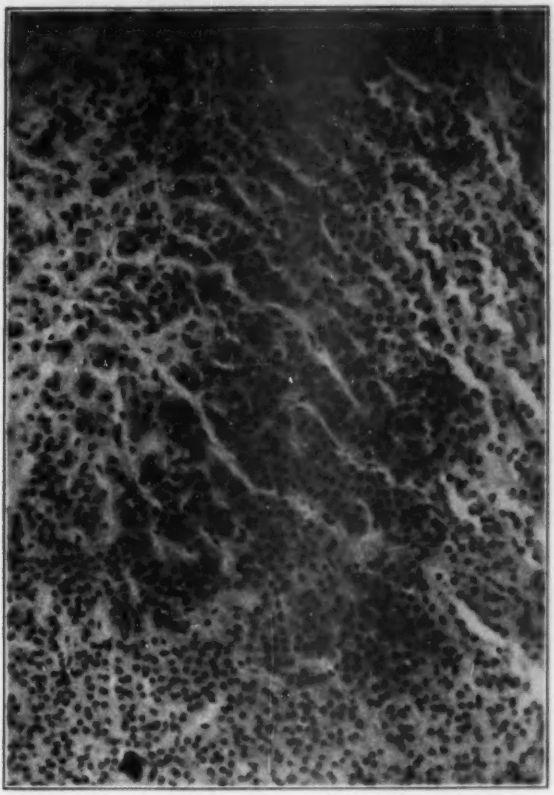

Fig. 3.—Normal adrenal cortex; × 115.

of the smaller black lesions were examined by biopsy on the twenty-second day of hospitalization. Sections from these lesions revealed a rather marked increase in deposition of melanin in the basal layers of the epidermis compatible with changes seen in Addison's disease. This finding was not diagnostic, however, since generalized pigmentation of the skin with increase in melanin in the epidermis is seen in many other systemic conditions and also as a terminal manifestation, either local or general, of various dermatoses.

Significant laboratory data included the following: Results of one spinal fluid examination, two urinalyses and three complete blood counts all were within normal limits except for a spinal fluid sugar content of 25 mg. per hundred cubic centimeters. The serum calcium level was 11.5 mg. per hundred cubic centimeters; serum chlorides, as sodium chloride, were 413, 165 and 429 mg., and total protein,

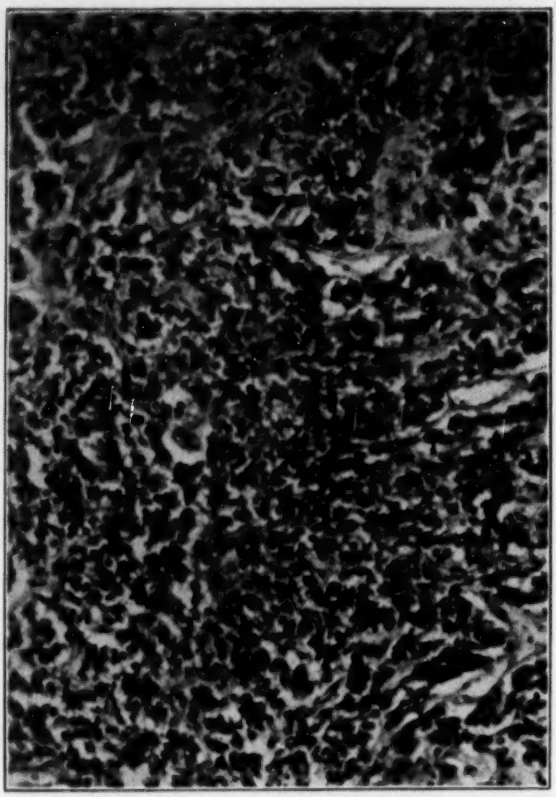

Fig. 4.—Pronounced distortion of the adrenal cortex of the patient; × 115.

9.40 mg. per hundred cubic centimeters. Fifteen daily fasting blood sugar values ranged from 35 to 183 mg. per hundred cubic centimeters, with an average of 76 mg., and six blood sugar values obtained three to four hours after a carbohydrate meal ranged from 56 to 87 mg. per hundred cubic centimeters, with an average of 75 mg. per hundred cubic centimeters. Roentgenograms of the abdomen and chest disclosed no evidence of pathologic changes, and an electrocardiogram was interpreted as normal.

In view of the appearance of new pigmented skin lesions, the progressive fall in blood plasma chlorides and the elevated total protein of the blood, the diagnosis of Addison's disease seemed difficult to exclude. Hence, 2 cc. of adrenal cortex extract in conjunction with 3 Gm. of enteric-coated sodium chloride tablets for oral use were again administered from the twenty-eighth to the thirtieth day of hospitalization. During that time the patient lapsed into a semicomatose state, appeared lethargic, vomited several times, became comatose and suddenly ceased breathing.

Summary of Necropsy Observations.—The body was that of a malnourished white boy. There were approximately fifty small darkly pigmented spots, most of them about 1 mm. in diameter, scattered over the skin of the entire body. The subcutaneous fat was colored a deeper yellow than is usually seen.

The outstanding feature was the size and appearance of the adrenal glands. The right weighted 540 mg. and the left 448 mg. These weights are approximately one fifth of the expected normal weights for a child of this age. Microscopic examination revealed a marked distortion of the usual cortical architecture. There was no remnant of the stratification of the cortical cells. The connective tissue septums were present, and the vessels appeared prominent. The cells enclosed in the septums contained dark-staining pyknotic nuclei, and the cytoplasm was ragged and appeared to be disintegrating. Areas of minimal infiltration of the connective tissue with lymphocytes were scattered throughout the sections. Figures 4 and 5 compare a normal adrenal cortex with that in the reported case.

Other significant findings were the prominence of the lymphoid tissues as evidenced by a large thymus gland, moderate enlargement of the lymph nodes, with an increase in the number of germinal centers, and hyperplasia of the lymphoid elements of the spleen and intestinal tract.

SUMMARY

A case of Addison's disease due to bilateral adrenal cortex atrophy in a 5½ year old boy is presented. This condition is extremely rare in the pediatric age group.

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IMMATURE CELL ERYTHREMIA

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AND
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PITTSBURGH

In the case to be described, enormous numbers of nucleated erythrocytes were present in the circulating blood and bone marrow initially and not only persisted unaffected by treatment but progressively increased in numbers. An associated proliferation of the immature cells characteristic of leukemia was absent. So far as could be ascertained, this blood dyscrasia was not initiated by or associated with hemolysis and was not related to erythroblastosis fetalis, Mediterranean anemia (hereditary leptocytosis) or sickle cell anemia. Such a condition may be designated as an erythremia or, possibly, more aptly as an erythroblastemia.

The continued presence of nucleated erythrocytes in large numbers in the circulating blood has not been reported frequently. In infants and children nucleated red blood cells sometimes have been observed in hemolytic anemias, hemophilia, hemorrhagic disease of the newborn, hereditary leptocytosis and leukemia. Children are occasionally seen in whom erythroblasts transiently form the majority of nucleated cells in both the peripheral circulation and the bone marrow in the early stages of leukemia, but as the leukemia progresses the nucleated red cells are displaced by cells typical of the leukemia.

REVIEW OF THE LITERATURE

Excluding the blood diseases already mentioned as not pertaining to our case, we have been unable to find in the literature any other instance of a blood dyscrasia in which the hyperplasia was confined to the red cell series, with an increase of only the immature erythroblasts in circulating blood, bone marrow and various organs.

There remain for consideration the erythroblastoses associated with leukemia.

In 1900 von Leube[1] described a rapidly progressive blood dyscrasia which showed characteristics of both pernicious anemia and myelogenous leukemia, and to this condition he applied the name "leukanemia." It may be that both pernicious anemia and leukemia were present in his patient, because such cases were later reported by many authors. Di Guglielmo,[2] in 1917 and in 1920, noted simultaneous increases of red blood cells, white blood cells and thrombocytes (platelets) and considered this condition to be the result of the action of a single agent influencing multipotential monoblasts (hemocytoblasts) and promonocytes (hemohistioblasts). He subdivided these erythroleukemias into "complete" and "incomplete." In the complete there is a numerical increase in the circulating mature leukocytes,

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1. von Leube, W.: Rapide verlaufende schwere Anämie mit gleichzeitiger leukämischer Veränderung des Blutbildes, Berl. klin. Wchnschr. **37**:851, 1900.

2. di Guglielmo, G.: Ricerche di ematologia, Folia med., Napoli **3**:386, 1917; Eritroleucemia e piastrinemia, ibid. **6**:1, 1920.

erythrocytes and thrombocytes, whereas in the incomplete there is anemia instead of polycythemia. In 1936, Smith and Silberberg [3] described, in a man of 52 years, a multiple myeloma consisting of a mixture of lymphocytes, plasmacytes, immature red cells and lymphoblasts (hemocytoblasts). The last-mentioned cells they believed to be the progenitor cells.

Israels,[4] in 1949, reported a case of immature cell erythremia in an adult in whom not only enormous numbers of immature erythrocytes but also many immature white cells were present. Stransky and Quintos [5] reported an erythroblastic leukemia associated with a striking erythroblastosis in a child.

REPORT OF CASE

A. H. B., a 2½ year old boy, was admitted to the Children's Hospital of Pittsburgh on Dec. 13, 1948, with a complaint of fever, loss of weight, pallor and protuberant abdomen. His family history was noncontributory. The father was of Dutch-Irish descent and the mother of Polish ancestry, but both parents were born in the United States. The childhood history was not unusual until Oct. 23, 1948, when he contracted a "cold" accompanied with a temperature reaching 104.8 F. and a painfully itchy skin.

On October 30 he was admitted to the Sewickley Valley Hospital. Here physical examination revealed a dulness in the right side of the chest which was first diagnosed as pneumonia and subsequently as a pulmonary abscess. The child was given penicillin, with considerable improvement in the condition. He was discharged on December 4, with a diagnosis of unresolved pneumonia with possible pulmonary abscess. Because of a rapidly progressing anemia, he was readmitted to the same hospital on December 29, and at this time the many blast forms in the blood and marrow smears suggested a diagnosis of leukemia.

On admittance to the Children's Hospital of Pittsburgh, physical examination showed all the superficial lymph nodes enlarged to an average diameter of 7 mm. The child had a mild tonsillitis and an enlargement of the liver, which extended 6 cm. below the costal margin in the midclavicular line. The spleen was markedly enlarged and reached to the pelvic brim. The diaphragm was pushed upward by these enlarged organs. In the right midportion of the chest posteriorly there was an area of dulness, with bronchial breathing and crepitant rales. The other organs appeared normal.

Roentgenograms of the chest showed a shadow involving the upper lobe of the right lung, but this shadow was thought not to represent an abscess. Decalcification of the long bones was also noted.

The blood was sterile on a culture. Repeated urinalyses gave negative results. Chemical studies on the blood gave the following values: nonprotein nitrogen, 30 mg. per hundred cubic centimeters; icteric index, 8.0; blood cholesterol, 121 mg. per hundred cubic centimeters; cephalin flocculation reaction negative in forty-eight hours; total serum protein, 4.94 Gm. per hundred cubic centimeters (albumin 3.26 Gm. and globulin 1.68 Gm.). Agglutination reactions were negative for Salmonella typhosa, Salmonella paratyphi A and B, Brucella abortus and Pasteurella tularensis. Tuberculin in a 1 to 10,000 dilution, histoplasmin and moniliin skin

3. Smith, R. P., and Silberberg, M.: Multiple Myeloma of Hemocytoblastic Type, Arch. Path. **21**:578 (May) 1936.

4. Israels, M. C. G.: Immature Cell Erythraemia in Adult, J. Path. & Bact. **48**:299, 1939.

5. Stransky, E., and Quintos, F. N.: Erythroblastic Leukemia, Am. J. Dis. Child. **62**:577 (Sept.) 1941.

TABLE 1.—*Blood Counts with Differential Counts*

Date	Red Blood Cells, Millions per Cu. Mm.	Hemoglobin %	Hemoglobin Gm.	White Blood Cells, Thousands per Cu. Mm.	Nucleated Red Cells, Thousands per Cu. Mm.	Monocytes, %	Percentage of Nucleated Red Cells: Normoblasts: Basophilic	Normoblasts: Polychromatic	Normoblasts: Orthochromatic	Pronormoblasts	Megaloblasts	Thrombocytes, Thousands per Cu. Mm.	Reticulocytes, %	Transfusions of Whole Blood, Cc.
1948						Sewickley Valley Hospital *								
11/ 1	3.38	58	...	1.7	....	82	....	....	....	....	....	...	...	500
11/13	3.74	67	...	2.8	....	53	....	....	....	....	....	...	...	500
11/29	4.61	86	...	22.8	....	42	....	....	....	....	....	...	...	...
12/29	2.36	40	...	29.5	....	Immature cells	....	....	....	....	....	10.4	...	...
1949						Children's Hospital of Pittsburgh								
1/ 3	1.65	..	4.8	7.05	7.90	..	9.4	39.5	13.7	....	37.6	120	...	150
1/ 8	2.40	..	8.0	0.34	0.56	..	19.2	10.8	2.4	31.4	36.2	120	0.8	625
1/12	2.09	..	6.8	0.90	2.70	..	17.4	8.1	....	34.6	39.9	68	...	300
1/18	2.56	..	8.5	6.00	6.20	..	26.9	9.2	1.3	38.6	24.0	....	...	300
1/24	3.20	..	10.5	4.20	6.30	..	53.7	8.3	3.2	3.4	31.4	200	...	375
1/30	3.08	..	9.2	9.80	14.70	..	33.8	30.8	6.2	10.8	18.4	132	3.5	125
2/12	1.35	..	4.7	7.74	78.30	..	12.1	30.8	18.7	12.1	36.3	114	...	375

* These values were obtained through the assistance of Dr. John Ungar Jr., pathologist at the Sewickley Valley Hospital.

test elicited negative reactions. Throat culture yielded a Streptococcus of the viridans group and pneumococci. Stool examination elicited negative results for ova and parasites. The child had type O_1 Rh-positive blood; the child's mother had Rh-positive blood.

Red cell counts ranged from 1,350,000 to 3,200,000 per cubic millimeter and hemoglobin from 4.7 to 10.5 Gm. per hundred cubic centimeters, and the only appreciable influencing factor was the transfusion of whole blood. Red cell fragility was within the normal range. The thrombocyte count varied from between 68,000 and 200,000 per cubic millimeter, and the higher count was obtained at the time the red cells were at their maximal level. In the blood the number of nucleated cells, which was 7,050 per cubic millimeter immediately after admission, dropped precipitously after 1 mg. of aminopterin (4-aminopteroylglutamic acid) was given daily on Jan. 1, 2 and 3, 1949, and then returned to its original level in about ten days. Terminally the nucleated cell count reached a maximum of 86,040 per cubic millimeter of blood. Of this number about 90 per cent belonged to the erythrogenic series. The prorubricytes (megaloblasts) and early immature rubricytes (normoblasts) outnumbered the more mature rubricytic elements. Furthermore, the remaining granulocytic cells were of the mature type (table 1).

TABLE 2.—*Percental Value of Bone Marrow Cells**

Date	Megaloblasts	Pronormoblasts	Basophilic Normoblasts	Polychromatic Normoblasts	Orthochromatic Normoblasts	Smudge Forms	Promyelocytes	Myelocytes	Metamyelocytes	Neutrophils	Eosinophils	Basophils	Monocytes	Lymphocytes	Undifferentiated	Total Nucleated Red Cells (Including Smudges)
1/3	11.6	16.4	15.4	12.2	4.0	24.8	0.4	0.4	2.8	3.2	0.8	...	0.4	6.8	0.8	84.4
1/18	0.2	2.0	1.6	22.2	24.9	34.3	...	...	0.2	0.5	...	0.4	0.4	11.2	...	86.0
2/16	10.0	9.2	6.0	10.0	20.8	19.7	...	0.4	1.2	2.6	...	0.4	...	5.0	1.1	88.6

* Each count included 500 cells.

The percental distribution of the cells in the two sternal marrow specimens obtained by puncture during life and in the marrow removed from a rib at autopsy were shown in table 2. The smudge forms were included in the differential count of the bone marrow and classified in the final evaluation as prorubricytes (megaloblasts) because of the fact that in many of them the outlines of nucleoli were still evident. Furthermore, practically no immature cells of the lymphocytic or granulocytic (myelocytic) series were present.

The temperature fluctuated widely, ranging between 104 F. and normal, and was influenced only by streptomycin.

It was initially thought the child had leukemia because of the many blast forms in the blood smears and the physical findings, and he was therefore treated with 1 mg. of aminopterin daily for three days before our first sternal marrow puncture was performed. The diagnosis of leukemia was then discarded, and it was realized that the condition primarily involved the red blood cells. The aminopterin was replaced with folic acid and penicillin in a daily dosage of 20 mg. and 300,000 units respectively. On the ninth hospital day streptomycin in a dosage of 0.5 Gm. twice daily was added, and within forty-eight hours the temperature rose to 103 F., but roentgenograms showed that the shadow in the right lung had lessened. Another course of streptomycin, begun on January 24, reduced the temperature to normal for a week. At this time the fever returned, and, although use of the drug was

continued, a septic type of fever continued until death, on February 16. During the hospital stay there was a steady loss of weight from 26 to 20 pounds (11.8 to 9.1 Kg.). While in the hospital, the child received a total of 21,075 cc. of whole blood, 10,200,000 units of penicillin and 13 Gm. of streptomycin without any permanent benefit.

An autopsy was performed four hours after death. The body was that of a 2 year old white boy, measuring 98 cm. in length. The anatomic observations were limited to lesions associated with extramedullary hemopoiesis; only these will be

Fig. 1.—Lung tissue with large artery in central area and several smaller arteries surrounded by mantles of erythropoietic tissue; × 40.

described. The skin was pale and spotted with petechiae, which were most numerous over the lower part of the abdomen. The heart was markedly enlarged and filled the middle half of the thoracic cavity. The pericardium was distended with about 100 cc. of clear straw-colored fluid. The heart showed a few petechiae over the left ventricle near the anterior coronary artery and an occasional small hemorrhage over the right ventricle. The adhesions binding the right lung to the chest wall were broken up with difficulty. The lungs on removal appeared somewhat congested and had a scattered subpleural red mottling. On section both lungs showed discrete consolidated areas, especially around the larger vessels. In addi-

tion, the right lung had a wedge-shaped denser area with the base of the wedge, measuring 20 mm., at the pleura and the apex at the hilus. This area had a yellowish and somewhat corrugated appearance but did not feel definitely fibrotic. When the abdomen was opened, the liver was noted to extend about 5 cm. below the costal margin in the midclavicular line. The liver weighed 920 Gm. and had a pale yellow color suggesting fatty infiltration. The distended gallbladder measured 4.5 by 2 cm. and was filled with green viscid bile. The spleen was markedly enlarged, weighed 420 Gm. and occupied a large part of the abdomen. On sectioning, it appeared edematous and congested. The stomach was small and con-

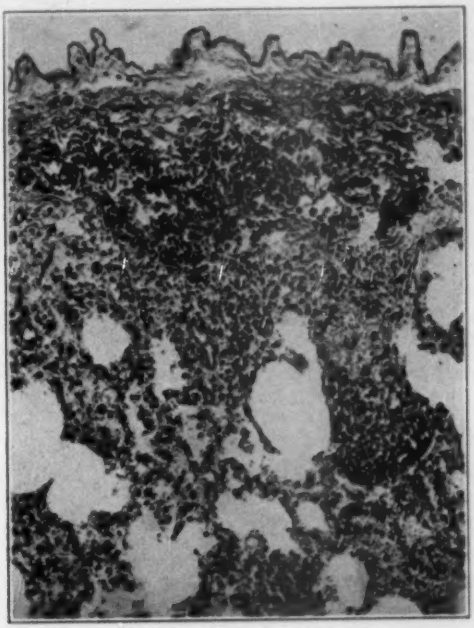

Fig. 2.—Island of hemopoietic tissue in pleura and the adjoining lung and scattered foci of developing red blood cells in the subjacent lung; × 175.

tained a considerable amount of mucus which in places was stained brownish with blood from small hemorrhages along the rugae. The peritoneal covering of the small intestine showed small scattered islands of congestion. The kidneys were interesting because of the presence on the cut surface of small linear streaks of congestion or hemorrhage extending from the pelvis toward the cortex. The adrenal glands showed nothing of interest.

Microscopically, the most conspicuous feature was extramedullary foci of hemopoiesis in practically all tissues of the body. These areas were found in greatest amounts in the bone marrow, lungs, spleen, lymph nodes and kidneys. In the lungs, the hemopoietic areas encircled the pulmonary arteries and arterioles in

wide zones (fig. 1) and also occurred in scattered linear foci throughout the pleura (fig. 2). It was impossible to tell whether any lesions of primary atypical pneumonia of unknown origin were present because of the ubiquitous islands of hemopoiesis. In the heart, in and around some of the coronary vessels, were seen small areas of hemopoiesis. The architecture of the spleen was completely lost and no malpighian corpuscles were recognizable. Islands of hemopoietic activity in which were grouped large numbers of immature cells were irregularly distributed throughout the organ, and intervening between these areas were diffusely scattered vast numbers of nucleated red cells in varying stages of immaturity. The

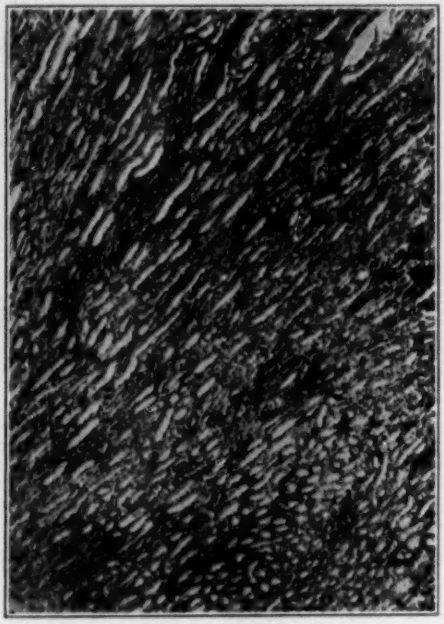

Fig. 3.—Linear streaks of hemopoiesis in arteriolae rectae of a kidney; × 40.

sinusoids were filled with these cells, which had also infiltrated the reticuloendothelial tissue. It was difficult, except in rare instances, to trace definitely the development of the erythroblasts in situ from splenic cells. A similar histologic picture was observed in the lymph nodes. Unfortunately, blocks of tissue were not removed from the liver. Small areas of hemopoiesis were scattered throughout the submucosa and serosa of the stomach and small intestine. In the kidney linear streaks of blood-forming tissue occurred in considerable numbers in and around the arteriolae rectae of the kidney (figs. 3 and 4). Such areas were most prominent in the medulla and among the collecting tubules. There were aggregates of hemopoietic tissue among the proximal tubules surrounding the glomeruli (fig. 5). The progressive development of the cells of the erythrocytic series from

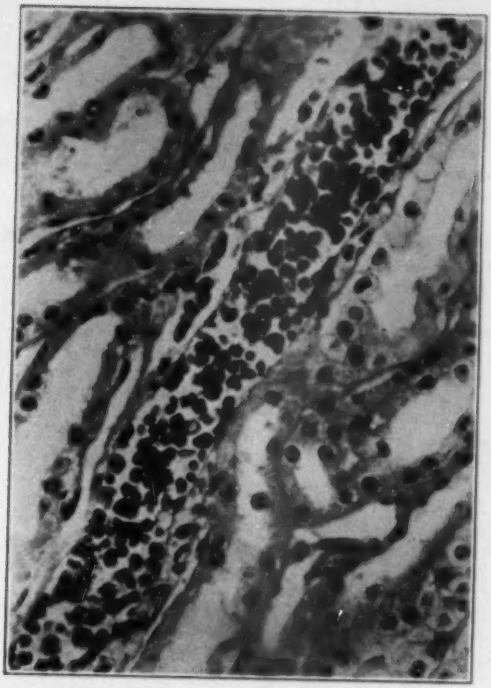

Fig. 4.—Developing red blood cells in one of the arteries shown in figure 3; × 375.

Fig. 5.—Developing red blood cells in the vicinity of a glomerulus; × 175.

vascular endothelium could be readily followed in these various vascular sites. Small hemopoietic foci were also demonstrated in the capsule and septums of the pancreas and adrenal glands, in the walls of the bladder and in the dermis.

COMMENT

The factor or factors responsible for the genesis of the blood dyscrasia in this child could not be determined.

There was no increased production of circulating erythrocytes and so far as could be determined no mechanism—e. g., pulmonary arteriosclerosis or congenital heart disease—which might give rise to an increased production. In contrast, our patient presented an anemia with numerous circulatory early nucleated red blood cells, which are absent in typical erythremia.

No history of hemorrhage or loss of blood at any time was elicited. The increased production of nucleated red cells was apparently not occasioned by concomitant leukemia, because at no time was there any indication of the hyperplasia which accompanies this condition. Clinical manifestations of an acute hemolytic anemia were absent. No tests were made for the hemolysis of acquired hemolytic anemia. The increased pigmentation, frequently accompanying intense or prolonged hemolysis, was lacking in spleen, lymph nodes and bone marrow. It is significant that the repeated transfusions had almost no influence on the maintenance of the blood level and did not alter the picture of the bone marrow or materially increase the reticulocyte level.

Myeloblastic (hemocytoblastic) myeloma can be ruled out because of the absence of localized bone lesions and the presence of marked hepatosplenomegaly with great numbers of nucleated erythrocytes in the peripheral circulation in our patient.

We have been unable to fit this case into any of the recognized classifications of blood dyscrasias. We believe that the condition might be due to an inhibitory mechanism interfering with erythrocyte maturation and acting at an earlier level than that giving rise to pernicious anemia. It also occurs at a later age than the megaloblastic anemia of infancy reported on by Zuelzer and Ogden.[6] Clinically and hematologically the condition was not identical with Mediterranean anemia (hereditary leptocytosis).

SUMMARY

A blood dyscrasia characterized by the continuous presence of a large number of immature nucleated erythrocytes in the circulation and bone marrow without manifestations of leukemia or obvious evidence of hemolytic anemia was studied in a white boy of 2½ years. The condition was resistant to therapy, was progressive in nature and proved fatal.

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6. Zuelzer, W. W., and Ogden, F. N.: Megaloblastic Anemia in Infancy: A Common Syndrome Responding Specifically to Folic Acid Therapy, Am. J. Dis. Child. **71**:211 (March) 1946.

BIPARTITE NAVICULAR BONE AS A CAUSE OF FLATFOOT

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Refractory flatfoot, particularly in children before the age of 8 or 9 years, is sometimes due to a supernumerary bone. Some of these bones undoubtedly cause symptoms of, or predispose to, flatfoot. In some hypertrophic arthritis develops in the true joint space. Surgical removal is thus often indicated.[1]

When the roentgenogram of the navicular bone shows an unusual condition, one should consider the possibility of a developmental variation.[2] That such an anomaly is by no means a rare occurrence was pointed out by Schindler and Gnagi.[3] In their experience, they found an 8 per cent occurrence of painful, divided navicular bone of the foot. The smooth contour and linear margin of density on the opposing surfaces eliminate the diagnosis of fracture of the navicular bone. Divided navicular bone is a bilaterally occurring anomaly. It develops as an ossification center of the navicular bone, which, instead of uniting normally with the body of the navicular, makes an independent development as an extra ossicle.

According to Lindgren,[4] in order that the roentgenologic diagnosis of bipartite navicular bone be made, the two bones at the site of the scaphoid must have a normal bony structure, and the two opposing surfaces must be bordered by a narrow zone of corticalis of normal appearance.

In 1941, de Fine Licht [5] presented 4 cases of bipartite navicular bone. In 2 of his cases the anomaly was bilateral. All 4 cases showed arthrotic changes in the joints. This author stated the opinion that the condition is a congenitally determined developmental abnormality.

REPORT OF A CASE

A. Van H., an 11 year old white girl, while jumping from roof to roof, fell on a fence, sustaining fractured ribs, contusions and subcutaneous emphysema. She was treated in the hospital with bed rest, penicillin and sulfadiazine. In spite of chemotherapy and biotherapy, transient bronchopneumonia developed.

On the tenth hospital day she complained of pain in the arches of her feet, although these areas were not involved in the injuries. Physical examination revealed evidence of pes planus bilaterally.

1. Cravener, E. K., and MacElroy, D. G.: Supernumerary Tarsal Scaphoids, Surg., Gynec. & Obst. **71**:218 (Aug.) 1940.

2. Childress, H. M.: Fracture of a Bipartite Carpal Navicular, J. Bone & Joint Surg. **25**:446 (April) 1943.

3. Schindler, J. A., and Gnagi, W. B. Jr.: Painful Divided Navicular of the Foot: Its Diagnosis and Treatment. Surgery **7**:133 (Jan.) 1940.

4. Lindgren, E.: On Os Naviculare Bipartitum, Acta radiol. **22**:511, 1941.

5. de Fine Licht, E. : On Bipartite Os Naviculare Pedis, Acta radiol. **22**:377, 1941.

Roentgenograms revealed prominence of the tuberosity of the right navicular bone. An accessory navicular bone appeared to be joined with the main body of the right navicular bone.

No active treatment was given. The symptoms disappeared spontaneously in a short time.

SUMMARY

A case of pes planus in an 11 year old white girl is presented. In this instance the deformity was due to a bipartite navicular bone. The importance of this presentation lies in the fact that the condition is common but not usually recognized by the physician ordinarily caring for children, particularly those children with refractory flatfoot.

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LARGE OVARIAN CYST IN A NEWBORN INFANT *

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ALLEN SCHULTZ, M.D.
AND
ALFRED A. STRAUSS, M.D.
CHICAGO

An abdominal mass in the neonatal period is infrequent. When such a mass is recognized, either because it produces symptoms by virtue of encroachment on adjacent organs or other structures or because of its large size it becomes palpable, surgical intervention is necessary. Because abdominal tumors in infants often are malignant, early diagnosis is of paramount importance. Newhauser [1] recently stated, in discussing the survival rate in cases of embryoma of the kidney, the commonest neoplasm of infancy, that cure following surgical removal decreases in frequency when diagnosis is delayed until after the first year of life.

We wish to report a large ovarian cyst as a rare cause of abdominal tumor in the newborn period. An abdominal mass was discovered in an infant at 4 days of age, and an exploratory operation was performed when the infant was 32 days old. A search of the literature leads us to believe that this is one of the youngest infants operated on from whom a large ovarian cyst was removed.

REPORT OF A CASE

D. O., a white girl 30 days of age, was admitted to Sarah Morris Hospital on Oct. 18, 1949 for an exploratory operation because of a large abdominal mass discovered at the age of 4 days by Dr. John Horowitz, of Kankakee, Ill.

From birth, the infant vomited after each feeding and did not have a bowel movement during the first three days of life. The infant was born at term, delivery was spontaneous and she appeared normal. The birth weight was 7 pounds 15 ounces (3,600 Gm.). She was fed an evaporated milk mixture and vomited frequently after feedings. However, the vomiting was not severe and at no time projectile. She had her first stool on the fourth day, and subsequently vomiting stopped. She was examined by Dr. Horowitz for the first time on the fourth day of life, and a mass was palpated in the right lower quadrant. A roentgenogram taken on the eighth day revealed absence of gas shadows in almost the entire right side of the abdomen and displacement of the intestines upward and to the left, suggesting a large tumor filling the greater part of the abdomen (fig. 1).

At the time of admission to Sarah Morris Hospital, physical examination revealed a well developed and fairly well nourished female infant weighing 8 pounds 13 ounces (3,990 Gm.). She did not appear ill. The only significant abnormalities were confined to the abdomen. There was a definite bulging in the right lower quadrant, which, on palpation indicated a large mass filling the entire right

* From the Sarah Morris Hospital for Children, Michael Reese Hospital.

1. Newhauser, E. B. D.: The Diagnosis and Rationale of Treatment of Neuroblastoma and Embryoma, read before the American Academy of Pediatrics, San Francisco, Nov. 15, 1949.

half of the abdomen. It was freely movable and felt cystic. A small amount of whitish mucoid vaginal secretion was observed. The genitalia otherwise appeared normal.

The red blood cell count was 5,200,000, the hemoglobin content 16.9 Gm. and the white cell count 13,200. The differential count revealed segmented polymorphonuclear granulocytes 26 per cent, nonsegmented cells 2 per cent, eosinophils 5 per cent, lymphocytes 55 per cent and monocytes 12 per cent. No abnormal cells were noted. Results of urinalysis were normal, and the blood urea nitrogen was

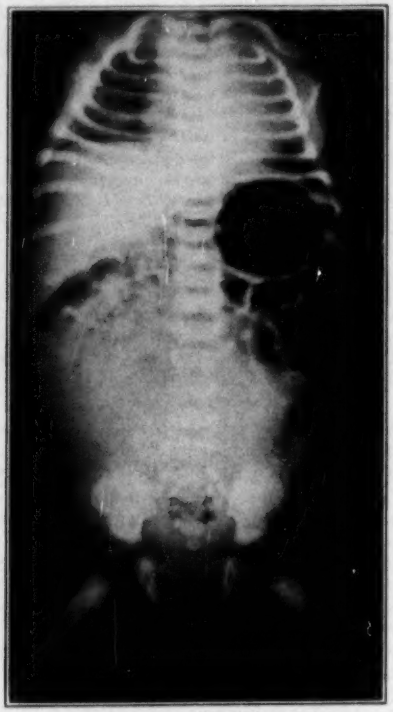

Fig. 1.—Roentgenogram taken on the eighth day of life showing absence of gas shadows in almost the entire right side of the abdomen and displacement of the intestines upward and to the left, suggesting a large mass filling the greater part of the abdomen.

19.3 mg. per hundred cubic centimeters. A vaginal smear revealed no evidence of estrogenic activity (Papanicolaou stain). It was our impression that the infant had a mesenteric cyst or possibly an embryoma of the right kidney.

On October 20, when the infant was 32 days old, an exploratory laparotomy was performed by one of us (A. A. S.). Under drop ether and local anesthesia, the peritoneal cavity was opened, and a large, grayish blue, tensely distended cyst

was visualized. The cyst was freely movable, was attached to a pedicle and filled almost the entire right side of the abdomen, displacing the abdominal contents upward and to the left as revealed on the roentgenogram (fig. 1). The cyst was the size of a fairly large grapefruit. Further exploration revealed that the cyst originated in, and entirely replaced, the right ovary. The left ovary appeared normal. The pedicle of the cyst was ligated and severed, and the right fallopian tube, which could not be preserved, was also removed. The postoperative course was uneventful.

Pathologic Report (by Dr. Otto Saphir).—Gross Description: The specimen consisted of a large, oval, cystic structure measuring 10 by 9 by 6 cm. (fig. 2). The capsule was thin, smooth and glistening, transparent and traversed by numerous thin vessels. The cyst contained a clear serous fluid. At one margin, which marked the possible site of the pedicle, the tissue was slightly thicker and more opaque

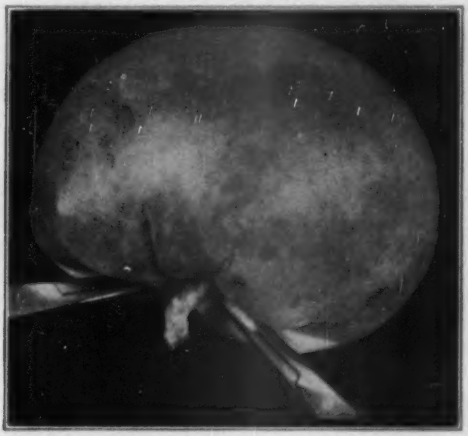

Fig. 2.—Large ovarian cyst (10 by 9 by 6 cm.) including the elongated pedicle. The cyst is distended with clear serous fluid.

than that of the capsule. After removal of the clamp, a thin tubular structure measuring 3 cm. in length was found attached to the thickened opaque area. The inner lining was smooth and glistening, and several small cysts were found in the region of the thick, opaque area.

Microscopic Description: One slide consisted of a cross section of a fallopian tube adherent to an opened cystic structure. This was composed of dense, fibrous connective tissue and compressed ovarian stroma. In the latter were blood vessels and occasional degenerated primary follicles. The lining of this cyst consisted of a thin layer of round cells covered by flat spindle-shaped cells (fig. 3). Within the wall and protruding into the cyst cavity were fairly large cysts apparently of follicle origin and containing an inner rim of imbricated round cells and an outer rim of polyhedral cells and fibroblasts (fig. 4). The cytoplasm of an occasional polyhedral cell was either vacuolated or clear. Another section consisted of ovarian tissue

Fig. 3.—Section of the large cyst showing the lining, consisting of a thin layer of round cells covered by flat, spindle-shaped cells. Hematoxylin and eosin; × 160.

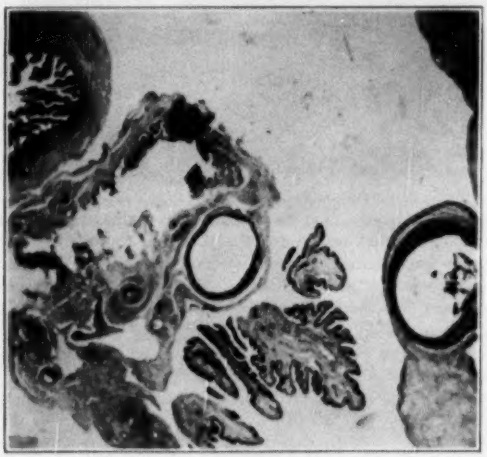

Fig. 4.—Section of the large cyst showing smaller cysts protruding into the cavity. They contain an inner rim of imbricated round cells and an outer rim of polyhedral cells and fibroblasts. Hematoxylin and eosin; × 48.

containing multiple follicle cysts of various ages, the majority consisting of an outer rim of fibroblastic cells and an inner band of imbricated round cells.

Microscopic Diagnosis: The histologic diagnosis was simple follicle cysts of the ovary.

COMMENT

Ovarian tumors are rare in children, particularly in infants under 1 year of age. A review of the literature reveals that the majority of cases reported are instances of ovarian cyst in which torsion of the pedicle produced acute symptoms, often leading to a preoperative diagnosis of acute appendicitis.

Downes [2] reported a case of simple cyst of the ovary in an infant 7 months of age. Up to the age of seven months a diagnosis of megacolon was considered on the basis of a progressive distention of the abdomen and obstipation. At 7 months roentgen studies of the colon with barium sulfate failed to confirm this impression, and an exploratory operation was performed. Witzberger and Agerty,[3] in a comprehensive review of the literature on ovarian neoplasms in children, covering the world literature up to 1937, collected 186 cases of ovarian tumors. Of these, 32 per cent were simple or multilocular cysts and 24 per cent were dermoids, sarcomas, carcinomas and teratomas comprising most of the rest. Only 7 of the 186 cases occurred in infants under 1 year of age. Of the 7, there were 3 cases of ovarian cyst; a multilocular cyst in an infant 2 months of age, a degenerated cyst in an infant 2 months of age and a multilocular cyst in a newborn infant. From 1937 to 1949, only two additional cases of ovarian cyst in a newborn infant were reported. In 1942 Bulformante [4] reported a cystadenoma of the ovary in an infant operated on at 36 days of age. In 1948 Neikirk and Hudson [4a] reported the successful removal of a follicular cyst of the ovary and fallopian tube in a 34 hour old infant. Abdominal distention and other symptoms and signs of intestinal obstruction were present. In 1949 Dargeon [5] reported 14 cases of ovarian tumors in children, collected from the surgical services of three large New York hospitals. In 5 of these cases the cysts were classified as dermoids, in 2 as follicular, in 1 as fimbrial, in 1 as paraovarian, and in 1 as pseudomucinous. The other 4 tumors were malignant teratoma, embryonal adenocarcinoma, choriocarcinoma and mesonephric adenosarcoma. The youngest patient of the entire series was 1 year of age, an infant with a mesonephric adenosarcoma. In 1949 Schaeffer and Veprovsky [6] reported 6 ovarian tumors in 6 children out of a total of 234 such tumors in 10,413 gynecologic admissions during a twelve year period. Only one patient was under 13 years of age—a 7 month old infant with a right-sided twisted dermoid cyst with hemorrhage, diagnosed preoperatively as intussusception. The remaining 5 tumors were in children 13 to 15 years of age and consisted of 2 dermoid cysts, 1 simple luteal cyst with hemorrhage, 1 pseudomucinous cyst and adenocarcinoma and 1 granulosa cell tumor.

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2. Downes, W. A.: Tumors of the Ovary in Children. J. A. M. A. **76**:443 (Feb. 12) 1921.

3. Witzberger, C. M., and Agerty, H. A.: Ovarian Tumors in Infancy and Childhood, Arch. Pediat. **54**:339, 1937.

4. Bulformante, J. C.: Large Ovarian Cyst in a Newborn Child, Am. J. Surg. **55**:175, 1942.

4a. Neikirk, W. I., and Hudson, W., Jr.: Giant Ovarian Cyst in a Newborn Infant, New England J. Med. **239**:468, 1948.

5. Dargeon, H. W.: Ovarian Tumors in Childhood, Pediatrics **3**:773, 1949.

6. Schaefer, G., and Veprovsky, E. C.: Ovarian Neoplasms in Children, Am. J. Obst. & Gynec. **58**:718, 1949.

It is not our purpose to discuss the various types and the pathology of ovarian tumors in infancy and childhood, because one can refer to the authoritative works of Novak [7] and Geist [8] for comprehensive treatises on this subject. However, based on Novak's classification,[8] cystic tumors of the ovary, other than follicle cysts, cystadenomas and dermoids are unlikely to develop in infancy. Of these, follicle cysts are by far the commonest. Although these cystic tumors are benign, all others appearing in this age group are solid tumors and are most frequently malignant. Therefore, early diagnosis and removal of the tumor are necessary.

Because of its rarity, ovarian cyst is rarely considered in the diagnosis of abdominal masses in the newborn infant. However, Ladd and Gross [9] have stated that cysts of the ovary may be found at birth, shortly afterward or at any period of childhood and are not uncommon in girls prior to puberty.

Conditions such as congenital intestinal obstructions from various causes, intussusception, enteric cysts, embryomas of the kidney, neuroblastomas and lesions of the kidney other than tumor, such as cystic disease and hydronephrosis, have been mistaken for ovarian cysts and tumors preoperatively. The fact that most large ovarian cysts have a relatively long pedicle, predisposing to mobility of the cyst, accounts for the frequency with which such cysts often ride out of the pelvis into the abdomen, so that the mass is thought to originate from some other organ, such as the mesentery or omentum.[9] Acute torsion of the pedicle is responsible for sudden onset of colicky pain and often fever with vomiting suggesting acute appendicitis, intestinal obstruction, ureteral colic or other condition. In the absence of acute symptoms, abdominal discomfort due to the large size of the cyst or symptoms arising as a result of encroachment on other organs may be significant. Often the cystic mass can be palpated rectally as well as abdominally. Roentgen examination of the abdomen with and without contrast medium for visualization of the intestinal tract and an intravenous urogram may be helpful in clarifying the diagnosis. However, regardless of whether or not an accurate diagnosis can be made, the presence of a persistent abdominal mass in the newborn period calls for early surgical exploration to exclude a malignant process.

CONCLUSIONS AND SUMMARY

A large ovarian cyst in a newborn infant is described. Symptoms of incomplete intestinal obstruction were present during the first four days of life. An intra-abdominal mass was palpated on the fourth day of life. An exploratory operation was performed on the thirty-second day of life and the cyst was removed.

Large ovarian cysts are rare in the newborn infant, but this diagnosis should be considered for all newborn girls with abdominal tumor. Because most abdominal tumors in infancy are malignant, early diagnosis and surgical intervention are indicated.

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7. Novak, E.: Gynecological and Obstetrical Pathology with Clinical and Endocrine Relations, ed. 2, Philadelphia, W. B. Saunders Company, 1947, p. 312.

8. Geist, S. H.: Ovarian Tumors, New York, Paul B. Hoeber Inc., 1942, pp. 449-451.

9. Ladd, W. E., and Gross, R. E.: Abdominal Surgery of Infancy and Childhood, Philadelphia, W. B. Saunders Company, 1941, p. 389.

Correspondence

POLIOMYELITIS OF THE NEWBORN

To the Editor:—In the July 1950 issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN, page 10, Baskin, Soule and Mills reported a case of proved poliomyelitis in a newborn infant with onset 3½ days after birth. In support of the possibility of intrauterine infection they cite "the fairly well established fact that the minimal incubation period of clinical poliomyelitis is five days." This "fact" is based on the papers of Aycock and Luther in 1929 and Casey in 1942. Unfortunately, they have overlooked the more recent paper by Horstmann and Paul (*J. A. M. A.* **135**:11 [Sept. 6] 1947) in which it is stated that "the interval between apparent exposure and the onset of clinical symptoms and signs has been observed to be as short as three and as long as thirty-five days, with many cases developing after a four to ten day period."

In case 1 of the Baskin report, with the 3½ day interval, there was not only opportunity for exposure at delivery but also some evidence suggesting the portal of entry. The mother was at the fourth day of the disease, a time that virus is usually present in the stools. Tracheal catheterization as well as insufflation was employed for resuscitation of the infant, whose subsequent symptoms were bulbar as well as spinal. If it is assumed that the mouth was contaminated at delivery, entry of the virus into the pharyngeal or laryngeal tissues might readily have been assisted by these procedures (catheterization, at least, being somewhat traumatic), from which bulbar (tenth cranial nerve) involvement could be anticipated.

I see no good reason that transplacental infection need seriously be considered in this case. The infrequency of blood stream invasion by poliomyelitis virus is attested by the large scale study of Ward, Horstmann and Melnick (which is cited by Baskin, Soule and Mills in support of their thesis), who recovered the virus from the blood only once in their series of 111 patients and who commented that "the rarity of the event . . . is in itself an indication of its probable lack of importance."

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To the Editor:—In his letter to the Editor, Dr. H. K. Faber stated that he could see no good reason that transplacental infection need seriously be considered in a case of poliomyelitis (case 1) reported in the July 1950 issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN by Soule, Mills and me. He noted that we believed the work of Aycock and Luther in 1929 and Casey in 1942 indicated that a five day minimum incubation period in poliomyelitis was a "fairly well established fact" and thought it unfortunate that we had overlooked the more recent paper by Horstmann and Paul, in 1947, in which they state three to 35 days were the extreme intervals between apparent exposure and the onset of clinical symptoms and signs "with many cases developing after a four to ten day period." The report by Horstmann and Paul was not overlooked but was omitted from our bibliography

for the following reasons: 1. It simply reviewed and interpreted the literature without adding new evidence concerning the clinical incubation period. Of the 14 articles tabulated by these authors, only two were interpreted as giving evidence of incubation periods of less than five days. 2. The minimal incubation period of three days was based on one of a number of cases reported by Fischer, Stillerman and Marks (Am. J. Dis. Child. **61**:305-321 [Feb.] 1941). This single case was one in which an acute febrile illness began three days after tonsillectomy. The diagnosis was nonparalytic poliomyelitis because of the presence in the cerebrospinal fluid of 75 cells per cubic millimeter, half of which were monocytes, and stiff neck and malaise. Fisher and his co-workers in no way even implied that this three day interval represented the incubation period of poliomyelitis, if that indeed was what it was. We did not believe Horstmann and Paul's interpretation sustaining evidence for a three day incubation period of poliomyelitis. 3. The second source of support for an incubation period of less than five days was Wernstedt (*Ergebnisse der inneren Medizin und Kinderheilkunde* **25**:705-820, 1924; **26**:248-350, 1924. This report was published earlier (1917) in the Swedish literature in one part. (Our translation was from the German reference listed.) Though he reported incubation periods of one to three days, Horstmann and Paul choose to ignore them. Possibly it was because most of these periods represented the intervals between the last of multiple exposures and the beginning of symptoms. Wernstedt thought *Fall IX* (case 9) an outstanding example of his *wahrscheinlich* or more accurately documented cases which proved that short incubation periods in poliomyelitis could occur "under unusual circumstances." In this "case" multiple cases of poliomyelitis occurred in a family, the first appearing on October 23, in a district which had had no poliomyelitis in one year. On October 24 a sailor from a neighboring village visited in the home. On October 27 the sailor's niece, living in his home village ½ mile (0.8 kilometer) from the family with multiple cases, became ill of poliomyelitis. We did not believe the information given in this and other cases convincing evidence of an incubation period of less than five days. He did report a case in which in both a mother and a newborn infant poliomyelitis developed on the fifth day post partum and stated that this supported a five day minimum incubation period.

We depended especially on the work of Casey because for the "first time on record a large number of single visits and exposures were available for plotting distribution of the incubation period."

Actually, the only group in which time of exposure can be definitely limited is the newborn. In no case of poliomyelitis in the newborn which I have found reported have symptoms or signs appeared before the fifth day of life unless the mother had been acutely ill of poliomyelitis beginning a few days before delivery. This has occurred in two instances known to us; one was case 1 of our report, and the other was a case report of Frovig (*Nord med.* **34**:1115 [May 9] 1947) which was overlooked in the original article. While his case is not documented with necropsy findings and animal passage studies, the clinical course was typical. It would seem an odd coincidence that in both reported instances of prodromes of poliomyelitis appearing in newborn infants before the fifth day of life the mothers should have acquired the disease a few days before delivery. Until future reports prove it a coincidence, we shall continue to believe it a reason for considering intrauterine infection in these two cases as well as contact infection.

Dr. Faber's numerous assumptions concerning the source of contact infection and portal of entry are all obvious possibilities. Biermann and Piszczek (*J. A. M. A.* **124**:296-297 [Jan. 29] 1944), cited in our original article, considered the possibili-

ties in a somewhat similar case to be (1) fetal infection, (2) birth canal exposure—essentially from feces, (3) contact exposure after birth from buccal, nasal or rectal secretions of mother and (4) other contact exposure.

Faber contends that blood stream invasion by the poliomyelitis virus is a rare occurrence because Ward, Horstmann and Melnick found it in but one of 111 patients. This may or may not be true, but Jungeblut (*J. Pediat.* **37**:109-128 [July] 1950) suggested a transient viremia as an integral part of a tentative sequence of events in the pathogenesis of poliomyelitis. He acknowledged this concept to be in "stark opposition to earlier beliefs [Faber, H. K.: Discussion of Poliomyelitis: Pathogenesis of the Early Stage, Proc. First Internat. Poliomyelitis Conference, New York, 1948] according to which the disease should be regarded as an essential and primary affection of the central nervous system."

For the reasons discussed above, we believe that intrauterine infection as well as contact infection should be considered seriously as a possibility in case 1 of our report.

JOHN L. BASKIN, M.D.
Mayo Clinic
Rochester, Minn.

News and Comment

GENERAL NEWS

Specialists Certified by American Board of Pediatrics, Inc.—The following physicians were certified as specialists by the American Board of Pediatrics, Inc. after examinations in Chicago on Oct. 13, 14 and 15, 1950:

Arnold Severen Anderson, Hopkins, Minn.; Charles R. Baker, Los Angeles; Alfred M. Bongiovanni, Drexel Hill, Penn.; Vernon Lee Branson, Beatrice, Neb.; Mark F. Canmann, Highland Park, Ill.; Leon L. Concepcion, Tarlac, Philippines; Henry H. Corn, Des Moines, Iowa; Peter J. Cotsirilos, Cicero, Ill.; William Grant Crook, Jackson, Tenn.; Ernest Samuel Cunningham, Jr., Fort Worth, Texas; Arthur Markham Dalton, Toledo, Ohio; Warren Robert Dammers, Winnetka, Ill.; Edward Rhiner Doezema, Kalamazoo, Mich.; Miles Edward Drake, Philadelphia; Emanuel Dubon, New York; William Grant Gilger II, Cleveland; Helen Martin Gilles, Lawrence, Kan.; Richard M. Greenwald, Forest Hills, N. Y.; Walter Moore Hart, Florence, S. C.; Mark Peter Holland, Mahanoy City, Penn.; Gerald E. Hughes, Kansas City, Mo.; George Wallace Kernodle, Burlington, N. C.; James Absolom Kinder, Jr., Cape Girardeau, Mo.; Nancy Burfoot King, Sandston, Va.; Kenneth A. Koerner, St. Louis; James B. Lawson, Denver; C. Ray Leininger, San Rafael, Calif.; Harold B. Levy, Shreveport, La.; Douglas Twichell Lindsay, Bismarck, N. D.; Ellen Pickard MacKenzie, Gretna, La.; George Anthony Maggio, Newark, N. J.; Robert A. Morris, Anderson, Ind.; George W. Nelson, Billings, Mont.; Arthur Hawley Parmalee, Jr., Pacific Palisades, Calif.; Paul Starrett Pierson, Milwaukee; George Bernard Rosenfeld, Buffalo; Joseph Leon Rosenzweig, Hot Springs, Ark.; Sidney S. Scherling, Minneapolis; Jerome Daniels Shaffer, Oklahoma City; Louis B. Silverman, Grand Forks, N. D.; Richard Mitten Steinberg, Downers Grove, Ill.; George K. Stephens, Ada, Okla.; John Alwin Sterner, Seattle; William A. Tanner, Madison, Wis.; Ben F. Thompson Jr., Baton Rouge, La.; Arthur L. Tuuri, Flint, Mich.; Douglas L. Wake, Royal Oak, Mich.; Lee Williamson, Abilene, Texas; Frank Sum Wissmath, Clayton, Mo.; Harry Hall Womack Jr., Fort Worth, Texas.

PERSONAL

Dr. Einor H. Christopherson Appointed Executive Secretary of American Academy of Pediatrics.—The Executive Board of the American Academy of Pediatrics announces the appointment of Dr. Einor H. Christopherson to the position of Executive Secretary to succeed Dr. Grulee. Dr. Christopherson will begin employment after the October meeting of the Academy and will serve with Dr. Grulee until the latter's retirement, July 1, 1951, when he will assume the full duties of this position.

Appointments of Dr. Orvar Swenson.—The Boston Floating Hospital, the pediatric teaching unit of the New England Medical Center, announces the appointment of Dr. Orvar Swenson as Surgeon in Chief on Oct. 15, 1950. Dr. Swenson has also been appointed Associate Professor of Surgery in the Tufts College Medical School.

ANNOUNCEMENTS

Fellowships in Pediatric Cardiology.—The pediatric cardiology department of the children's division of the Cook County Hospital is now accepting applications for fellowships for immediate appointment. The department offers large material of both congenital and acquired diseases of the heart. Over 500 cases of congenital malformations of the heart have been studied in the past three years. There is a complete department of angiocardiography and catheterization. The salary is commensurate with experience.

Please write to Dr. Rowine H. Brown, Assistant Medical Superintendent, Children's Division of the Cook County Hospital, 700 South Wood Street, Chicago 12.

Coming Examinations to be Held by the American Board of Pediatrics, Inc.—Written examinations under local monitors will be held by the American Board of Pediatrics, Inc. on Friday, Jan. 19, 1951 from 2:00 to 4:00 p. m. This is the only written examination which will be given during 1951.

The next oral examinations will be held in Boston, on Dec. 1, 2 and 3, 1950 and in New Orleans, on March 2, 3 and 4, 1951.

SPECIAL NOTICE

For the general information of indexers, catalogers and library personnel with reference to the listing of the new title of this journal, we advise that the *Quarterly Cumulative Index Medicus* policy be followed. The *Quarterly Cumulative Index Medicus* beginning with its volume 49 (January-June 1951) will list this journal under the new title, so that the letters A. M. A. will be included as an integral part of the title. For the completion of volume 48 (July-December 1950) the *Quarterly Cumulative Index Medicus* will continue to use the old title, without adding the designation A. M. A.

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

Modification of Proteinemia and Plasma Volume in Infantile Toxicosis. Eugenio Schwarz-Tiene and Pino Menghi, Helvet. pædiat. acta **2**:242 (June) 1947.

The authors, in continuation of their investigations on serum proteins and plasma volumes in infantile toxicosis, observed normalization of the hyperproteinemia which frequently accompanies hyperalbuminemia and hypoglobulinemia after plasma therapy. On rare occasions when hypoproteinemia exists with hyperalbuminemia, plasma transfusions also lead to normalization of the serum proteins. A mathematically simple method allows the changes in the plasma volume to be studied by means of continuous determination of the relationship between the erythrocytes and the plasma. The great advantages of plasma therapy in the hydration of infants and the normalization of the serum proteins and the toxicosis are thus corroborated.

From the Authors' Summary.

Problems of Infant Feeding. A. Flesch, Orvosok lapja **2**:1189 (Oct. 1) 1946.

In 1945, a high degree of hypogalactia and agalactia was observed by Hungarian pediatricians such as had never been seen before. Starvation and constant excitement of the mothers had caused this phenomenon. Since there was no milk at all, infants were fed with various mixtures of carbohydrates, which produced atrophy and edema because of deficiency in protein and fat. It was interesting that infants with atrophy gave the well known pathologic picture of desquamative erythroderma (Leiner). Cases of rickets increased owing to lack of antirachitic drugs. Later when the milk supply improved, preservation of its freshness was hindered by lack of ice. Vitamin C in the form of fresh vegetables and fruits was at hand; lemons were not obtainable. Infant feeding improved only in the autumn when the Western relief reached Hungary.

Görgényi-Göttche, Budapest, Hungary.

Examinations of Mother's Milk. R. Tarján, M. Molnár, L. Fekete and J. Sós, Orvosok lapja **3**:89 (Jan. 19) 1947.

In the Public Health Institute in Budapest, Hungary, samples of mother's milk were examined. The content of protein, fat and carbohydrates differed greatly. The caloric value of one mother's milk was, for instance, no higher than 22.5 calories per gram, whereas the value of one of the other samples was 110 calories per gram. This striking difference is not of great importance as long as the infant is suckling, for the gain or loss of weight shows whether the infant is starving or not. The situation is different when mother's milk is given by bottle. For such infants the procedure used in the dairy should be tried: the milk of various mothers should be mixed; thus, extreme differences may be avoided.

Görgényi-Göttche, Budapest, Hungary.

Hygiene; Growth and Nutrition; Public Health

Fetal and Neonatal Deaths in 4,117 Consecutive Births. Herbert C. Miller, Pediatrics **5**:180 (Feb.) 1950.

An analysis of the significant causes of death in 4,117 consecutive births was made; there were 66 fetal deaths and 85 neonatal deaths. A significant cause of death was determined for 51 fetuses and 56 liveborn infants.

Eighty-five per cent of the liveborn infants who weighed over 1,000 Gm. at birth and had postmortem examinations had causes of death which were considered to be significant. Almost half of the liveborn premature infants with birth weights between 1,000 and 2,500 Gm. were considered to have had more than one significant cause of death.

The so-called significant causes of death among liveborn infants differed from those determined for fetuses dying before birth. Among the former, pathologic conditions in the infants were determined four times as frequently as in those dying before birth, and in the latter maternal complications of pregnancy and labor were diagnosed as significant causes of death five times as frequently as in infants dying in the neonatal period.

Hyaline-like material in the lung was considereed to be the most frequent significant cause of death in liveborn premature infants; congenital malformation and anoxia resulting from complications of labor were the most frequently determined significant causes of death in liveborn full term infants. No differences were found in the significant causes of death in premature and full term fetuses. Anoxia resulting from accidental and unexpected interruption of the blood flow in the placenta and umbilical cord and from dystocia was the most frequently determined significant cause of death in both groups.

A plea is made for the adoption by obstetricians, pathologists and pediatricians of a formal uniform plan of classifying the causes of fetal and neonatal death which would divest current efforts to determine the cause of death of as much vague terminology and arbitrary opinion as possible.

From the Author's Summary.

Problems of the Public Nurseries and Children's Homes in Budapest, Hungary. J. Surányi, Orvosok lapja **3**:393 (March 23) 1947.

The demand for public nurseries and children's homes is steadily increasing in Budapest. The social circumstances and the need for mothers to work outside the home are making this demand more urgent. In Budapest, 387 infants and 2,864 children are placed in such homes, but the number of homes is not sufficient to meet the wants of the population. Well trained nurses are also too few.

The placement of sick infants and children meets with the greatest difficulties. Ill infants and children who do not need hospital treatment but who cannot be left among healthy infants and children should be placed in separate rooms of the nurseries or children's homes, where they can remain and be treated until they recover. Thus, working mothers could rest peacefully while their infants and children are cared for during their less serious illnesses.

Görgényi-Göttche, Budapest, Hungary.

Prematurity and Congenital Deformities

Two Cases of Congenital Diaphragmatic Relaxation, with Special Reference to the Position of the Gastrointestinal Tract. Hans Zellweger, Helvet. pædiat. acta **2**:227 (June) 1947.

Two cases of diaphragmatic relaxation are described. Both exhibited an abnormal position of the gastrointestinal tract; the stomach was turned upward, its axis horizontal so that the cardia was below, the greater curvature above and the duodenum before the stomach. The jejunum and ileum appeared to be normal. A secum mobile was observed. The ascending and transverse portions of the colon ran diagonally from the lower right to the upper left of the abdomen. The

hepatic flexure was lacking in one case and suspected to be so in the second. The diaphragmatic relaxation seemed to be present already while the primitive alimentary tube was still in the median plane. From this fact, the unusual position of the gastrointestinal organs may be easily explained.

FROM THE AUTHOR'S SUMMARY.

INFLUENCE OF SEASONS ON HEMORRHAGIC TENDENCIES OF NEWBORN INFANTS. O. KERPEL-FRÓNIUS, Orvosok lapja **2**:1253 (Oct. 15) 1946.

Kerpel-Frónius, in observing the large number of newborn infants at the gynecologic clinic in Budapest, found that hemorrhagic manifestations in newborn infants (melena neonatorum, cephalhematoma, cerebral and conjunctival bleeding) show a pronounced seasonal vacillation. Such conditions seem rare during the summer months but become more frequent in the autumn. The highest level was observed in the months from February to April. It may be that in the beginning of the summer an antihemorrhagic factor develops in the body which increases the capillary resistance and decreases clotting time. This so-called summer factor is perhaps identical with vitamin K, but vitamins C and P probably also are involved. The prothrombin content of the blood is less in winter and spring than during the summer and autumn. In the prevention of seasonal hemorrhagic tendencies, prenatal prophylaxis is most important. The best effect can be obtained when the mother receives vitamin K injections during the last ten days of pregnancy.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

Acute Contagious Diseases

MENINGOCOCCEMIA WITHOUT MENINGITIS: A REVIEW OF FIVE CASES. LUTHER L. TERRY and CHARLES W. JONES, Am. J. M. Sc. **214**:593 (Dec.) 1947.

Five cases of meningococcemia, 2 acute and 3 chronic, are reported, and the case histories are reviewed with reference to previously reported findings. The importance of laboratory studies in the diagnosis of meningococcemia is emphasized. Bacteriologic study of the skin lesions was found to offer a valuable rapid diagnostic method in suspected cases of the disease.

HENSKE, OMAHA.

BULBAR POLIOMYELITIS: ITS DIAGNOSIS AND TREATMENT. A. B. BAKER, Illinois M. J. **92**:160 (Sept.) 1947.

A recent study on 183 cases of bulbar poliomyelitis at the University of Minnesota hospitals is reported. The following classification of such cases is proposed: (1) the cranial nerve nuclei group, (2) the respiratory center group, (3) the circulatory center group and (4) the encephalitic group.

Suggested therapeutic measures are early elective tracheotomy, adequate use of suction of the pharynx and tracheotomy opening, administration of gas mixtures containing up to 40 per cent oxygen under positive pressure if pulmonary edema is expected, adequate humidification of the gas mixture, a careful checking of the oxygenation of the patient, frequent moving of the patient to avoid hypostasis and thrombophlebitis, maintenance of nutrition by nasal feeding, use of penicillin prophylactically, avoidance of the use of sedative drugs and stimulants, early closure of the tracheotomy opening and unceasing watchfulness.

BARBOUR, Peoria, Ill.

POLIOMYELITIS. ARCHIBALD L. HOYNE and PETER J. COTSIRILOS, Illinois M. J. **92**:164 (Sept.) 1947.

A review of 225 cases of poliomyelitis at the contagious disease department of Cook County Hospital in 1946 is given. One hundred and forty of the patients came from rural areas and 85 from Chicago. Thirty-six of the patients were 5 years of age or less. Thirty per cent of the rural children and 44 per cent of the urban ones were 5 years of age or less. Of all the patients, 54 per cent were male. Of the rural patients, 58.5 per cent were male, but only 45.8 per cent of the urban patients were male. There were 10 instances of more than 1 patient from the same family. Eight of the patients were pregnant.

There is no group of symptoms which can be classed as characteristic at the onset. An elevation in temperature should always be expected. As long as there is fever any existing paralysis may extend. If paralysis develops, it will make its appearance in three and one-half to four days in the majority of patients.

The principal complaints of the patients were, in the order of their frequency, fever, stiffness of the neck, headache, stiffness of the back, anorexia, vomiting, nausea, sore throat, listlessness and urinary retention. Two physical signs were almost invariably present: the head drop and stiffness of the neck or back. For treatment, hospitalization and rest in bed are important. For patients with the spinal type, use of hot packs and physical therapy is of value.

BARBOUR, Peoria, Ill.

THE BULBAR FORM OF POLIOMYELITIS: DIAGNOSIS AND CORRELATION OF CLINICAL WITH PHYSIOLOGIC AND PATHOLOGIC MANIFESTATIONS. THE MINNESOTA POLIOMYELITIS RESEARCH COMMISSION, J. A. M. A. **134**:757 (June 28) 1947.

Bulbar poliomyelitis is not a single clinical entity but can be divided into a number of clinical groups, depending on the region of the medulla involved by the pathologic process. The following classification was evolved to cover all cases of bulbar poliomyelitis:

1. Those in which the nuclei of the cranial nerves are involved
   (*a*) Upper cranial nerve group
   (*b*) Lower cranial nerve group

Only involvement of the tenth cranial nerve furnishes an immediate threat to the life of the patient by producing an obstruction to the airway.

2. Those in which the autonomic centers are affected
   (*a*) Respiratory center group
   (*b*) Circulatory center group
3. Those in which there is combined bulbar and encephalitic involvement
   (*a*) Diffuse encephalitic group
   (*b*) Focal encephalitic group

Deficient oxygenation and cerebral anoxia may produce cerebral symptoms in bulbar poliomyelitis.

4. Those in which bulbar involvement and involvement of the upper part of the spinal cord are combined.

BAIRD, Wauwatosa, Wis.

POLIOMYELITIS: NEUROPATHOLOGIC OBSERVATIONS IN RELATION TO MOTOR SYMPTOMS. DAVID BODIAN, J. A. M. A. **134**:1148 (Aug. 2) 1947.

This report on pathologic material obtained at autopsy from 24 human subjects with poliomyelitis, 2 of whom did not die of poliomyelitis primarily, illustrates the three features of the pathologic picture in the disease: 1. Every patient with polio-

myelitis exhibits lesions in the brain. 2. Some parts of the brain are seldom if ever affected; namely, the cerebral cortex except the motor area, the corpus striatum except the globus pallidus and the cerebellar cortex except the vermis. The brain stem as far forward as the hypothalamus and thalamus shows the chief involvement. The brain centers most frequently involved are the vestibular nuclei, the roof nuclei of the cerebellum and the reticular formation. Motor nuclei for the cranial nerves (third, fifth, seventh, tenth and twelfth) also showed frequent damage. 3. The variation is in the severity of the involvement, not so much in the extent of the involvement.

In the spinal cord the severest damage is always in the anterior portion of the column. The intermediate and posterior parts of the column may also be affected. The distribution of the pathologic lesions in the central nervous system has its manifestation in the clinical picture of the disease, both in the acute stage and in the convalescent period.

BAIRD, Wauwatosa, Wis.

DISSEMINATED CHICKENPOX (PNEUMONIA AND NEPHRITIS). CHARLES E. GRAYSON and ELIZABETH J. BRADLEY, J. A. M. A. **134**:1237 (Aug. 9) 1947.

A case of disseminated chickenpox with recovery in a white man, aged 34 years, is reported. The patient had clinical and roentgenologic evidence of pneumonia, the course of which coincided with that of his cutaneous lesions. The pneumonia did not respond to treatment with sulfadiazine or penicillin. Bacteriologic examinations gave negative results, as did cold agglutination tests, agglutinations for typhoid, paratyphoid and brucellosis and complement fixation tests for psittacosis. Hematuria and albuminuria developed on the 28th day in the hospital.

BAIRD, Wauwatosa, Wis.

BULBAR FORM OF POLIOMYELITIS: THERAPEUTIC MEASURES BASED ON PATHOLOGIC AND PHYSIOLOGIC FINDINGS. THE MINNESOTA POLIOMYELITIS RESEARCH COMMISSION, J. A. M. A. **135**:425 (Oct. 18) 1947.

During the 1946 epidemic of poliomyelitis, 183 patients with bulbar involvement were admitted to the University of Minnesota Hospitals, Minneapolis. Studies on this large group of patients revealed that bulbar poliomyelitis was not a single homogeneous entity but could be divided into four groups of symptom complexes, each pointing toward involvement of a specific region of the nervous system and requiring varying treatment procedures. The suggested therapies, correlated with the symptoms generally seen, were tabulated for each of the groups of bulbar poliomyelitis.

FROM THE AUTHORS' SUMMARY.

LOCAL TREATMENT OF CARRIERS OF VIRULENT DIPHTHERIA WITH PENICILLIN. A. J. LEVY, J. A. M. A. **136**:855 (March 27) 1948.

Four diphtheria carriers were discovered in the Dixon State Hospital at Dixon, Ill. All had been immunized, the first four months previously so that no Schick test had been done, the others three, four or five years previously. It was observed that administration of penicillin lozenges, 1,000 units each, every two hours for six days was effective, as compared with results in 1 control, in eliminating the carrier state. Also, 10,000 units of penicillin per cubic centimeter administered with an atomizer was effective in a nasal carrier. In the acute carrier penicillin given by any route is considered a poor detoxifying agent.

KIMBALL, Evanston, Ill.

THE PRESENT STATUS OF THE POLIOMYELITIS PROBLEM. VERNON W. LIPPARD, New Orleans M. & S. J. **100**:262 (Dec.) 1947.

The present status of knowledge of poliomyelitis is reviewed in regard to the causative organism, epidemiologic aspects, pathways of invasion, symptomatology and pathologic manifestations, prevention and therapy.

McGUIGAN, Evanston, Ill.

EPIDEMIOLOGY AND RECENT DEVELOPMENTS IN POLIOMYELITIS. JOSEPH G. MOLNER, New Orleans M. & S. J. **100**:408 (March) 1948.

Modern concepts of the manner in which poliomyelitis is transmitted and contracted are reviewed. Prophylaxis is as yet at a standstill, and no preventive measures are known.

McGUIGAN, Evanston, Ill.

IMMUNIZATION WITH COMBINED DIPHTHERIA AND TETANUS TOXOIDS (ALUMINUM HYDROXIDE ADSORBED) CONTAINING H. PERTUSSIS VACCINE: II. DURATION OF SEROLOGIC IMMUNITY. JOHN J. MILLER JR. and MARY LOUISE RYAN, Pediatrics **1**:8 (Jan.) 1948.

One hundred and twenty-six infants and children were given injections of combined diphtheria and tetanus toxoids (aluminum hydroxide adsorbed) containing Hemophilus pertussis vaccine, 20,000,000,000 organisms per cubic centimeter. Two injections were given with a twelve week interval. No reinjections were made in the four year period of observation.

Pertussis agglutinative reactions consonant with clinical immunity were obtained in 70 per cent of the subjects during the first year after the injections. In the subsequent four years serologic immunity waned in 40 per cent. High levels of tetanus antitoxin were demonstrated during the first year. From two to four years thereafter, 98 per cent of the subjects maintained levels of 0.1 unit or more. Such prolonged maintenance of high antitoxin titer has not been described previously as far as we are aware. Schick reactions were uniformly negative. Those children retested two to four years later also all reacted negatively. Diphtheria antitoxin titrations performed prior to Schick retests showed that 90 per cent of the subjects carried 0.1 unit or more.

Because it was felt that the serologic immunity against whooping cough in this group was not optimal, the routine was altered by increasing the dose of H. pertussis vaccine. Midway between the two injections of triple mixture, an injection of H. pertussis vaccine in saline solution was given. One hundred and three subjects given such injections have been observed for two and one-half years.

The addition of 40,000,000,000 or 60,000,000,000 H. pertussis organisms (to bring the total dose to 80,000,000,000 or 100,000,000,000 organisms) resulted in the production of high agglutinative titers in 84 per cent of the children. Results of tetanus and diphtheria antitoxin titrations in this second group of children were similar to those in the first group. No positive Schick reactions were observed.

FROM THE AUTHORS' SUMMARY.

THE AGE INCIDENCE OF POLIOMYELITIS IN CLEVELAND. HELMUT M. DEHN, Pediatrics **1**:83 (Jan.) 1948.

Recent statements from a number of countries have been made that the age incidence of poliomyelitis is moving upward. These have been challenged on the grounds that (1) this apparent trend may merely reflect the aging of the general

population and (2) diagnosis has become more accurate with the years and reporting more complete, especially for nonparalytic cases, so that old and new figures cannot be compared.

Accordingly, in an examination of the age distribution in Cleveland, the attack rate per 100,000 population in each age group was determined. Using information obtained in an analysis of the reporting of poliomyelitis in Massachusetts, the author confined the material to paralytic poliomyelitis originating in Cleveland in the second six months of the epidemic years 1930, 1941, 1944 and 1946. The elimination of nonparalytic cases, most of them undoubtedly never recognized and many falsely diagnosed, not only is statistically necessary but also serves to emphasize the distinct problem of the pathogenesis of paralysis, occurring as it does in only a minority of persons infected with the virus of poliomyelitis.

The number of cases occurring during the Cleveland epidemics, defined as already indicated, varied between 103 and 143. Since 1930, the peak of the age incidence has shifted from the group 0 to 4 years of age to the group 5 to 9 years of age. There was no significant change in the group aged 10 to 14 years. The attack rate among those over 15 has more than doubled but remains small compared with the incidence in the children under 10 years old.

These figures lend support to the impression gained from less stringently selected data from other parts of the United States and from certain foreign countries where poliomyelitis has been common for many years—that the incidence of poliomyelitis is gradually shifting from the small child to the older child and even toward the adult. It is further concluded that the name "infantile paralysis," is becoming obsolete, at least in these places and countries. However, it will not be overlooked that more than half the patients in Cleveland are still under 10 years of age, that the attack rate is generally at least twice as high in children under 10 as it is in the older children and that it tapers off rapidly at the adult age level.

FROM THE AUTHOR'S SUMMARY.

RECOVERY FROM COMPLETE HEART BLOCK IN DIPHTHERIA. MARY ALLEN ENGLE, Pediatrics **3**:222 (Feb.) 1949.

Six recoveries among 13 patients who had complete heart block during the course of severe diphtheria are reported. Four of the survivors also had disturbances in intraventricular conduction. Five who recovered had on admission extensive membrane formation and massive glandular and periglandular edema of the neck. Except for 1 patient admitted in the third week of disease, all received a large single dose of diphtheria antitoxin on arrival at the hospital. During convalescence 4 who recovered showed multiple pareses of peripheral nerves.

The onset of myocarditis was before the third week of illness. The duration of conduction disturbances was three to sixty days. Without an electrocardiogram the total auriculoventricular dissociation in several patients might have been overlooked, for the pulse in 5 was not abnormally slow and physical examination in 2 revealed only slight changes out of proportion to the severity of the electrocardiographic findings. On the other hand, 2 who recovered showed evidence of both congestive heart failure and peripheral vascular collapse. Digitalization was followed by prompt improvement.

FROM THE AUTHOR'S SUMMARY.

COMBINED IMMUNIZATION AGAINST DIPHTHERIA, TETANUS AND PERTUSSIS IN NEWBORN INFANTS: III. RELATIONSHIP OF AGE TO ANTIBODY PRODUCTION. PAUL A. DI SANT'AGNESE, Pediatrics **3**:333 (March) 1949.

A comparison was made of antibody production by newborn infants and by older children following prophylactic inoculation against diphtheria, tetanus and

whooping cough. In all instances the same triple-combined antigen was used, and the same routine was followed. The first injection of the vaccine was administered to all newborn infants at 7 days of age. Most of the "older" children were between 6 and 12 months of age at the first injection.

The incidence and severity of systemic reactions to administration of the triple-combined antigen increased with subsequent injections in newborn infants; the reverse was true of the "older" children. No such difference was noted between the two age groups in local reactions to inoculation. Five sterile abscesses were observed in the newborn infants and none in the "older" children. Pertussis agglutinin titers achieved after immunization were consistently higher (even after booster dose) in "older" children than in infants given the injections in the newborn period. "Older" children produced significantly higher diphtheria antitoxin titers after prophylactic injection than the newborn infants. After administration of a booster dose, however, diphtheria antibody production in the two age groups was comparable. No difference was found at any time in tetanus antitoxin levels achieved after inoculation by the newborn infants and the "older" children.

It was concluded that during the first year of life the capacity to produce antibodies in response to an antigenic stimulus increases with advancing age. It was felt, however, that in some instances the immunologic handicap due to tissue immaturity can be overcome if a sufficiently great antigenic stimulus is given.

Evaluation of antibody titers achieved by newborn infants after prophylactic injection of triple-combined antigen reveals that the results of immunization against tetanus and diphtheria were satisfactory. The results of inoculation against whooping cough were considered to be unsatisfactory, mainly because the proportion of infants who produced "protective" agglutinin titers fell far short of the 90 per cent which is the maximum that can be expected. A conservative approach to the problem of active immunization in early infancy is urged. It is suggested that until further work is done routine prophylactic inoculations should not be started before the age of 3 months.

FROM THE AUTHOR'S SUMMARY.

ACUTE SEROUS MENINGITIS AND ENCEPHALITIS COMPLICATING SCARLET FEVER. LEWIS K. SWEET, Pediatrics **3**:442 (April) 1949.

The syndrome of acute serous meningitis complicating scarlet fever is described. The condition has been observed in approximately 1 per cent of patients with scarlet fever. The onset usually is in the second half of the first week of illness. There is a recrudescence of fever, with headache, toxemia, meningeal signs, which may be minimal or absent, and a lymphocytic pleocytosis in the spinal fluid. The blood shows a polymorphonuclear leukocytosis in most instances. The condition ameliorates rapidly and recovery seems to be complete. The clinical manifestations of this syndrome are quite different from those of encephalitis complicating scarlet fever. The points in differential diagnosis are outlined.

FROM THE AUTHOR'S SUMMARY.

SUCCESSFUL TREATMENT OF C. DIPHTHERIAE SUBACUTE BACTERIAL ENDOCARDITIS WITH PENICILLIN AND STREPTOMYCIN. JOHN R. ALMKLOV and ARILD E. HANSEN, Pediatrics **5**:437 (March) 1950.

Corynebacterium diphtheriae is an unusual causative organism of subacute bacterial endocarditis, as only 17 cases have been recorded and in none of these has the patient survived. The 8 year old girl whose case is reported by Almklov and Hansen is the first patient to have recovered. This child had two positive blood cultures for a virulent intermedius strain of C. diphtheriae which was

sensitive to 0.05 microgram of penicillin and to 3.0 micrograms of streptomycin per milliliter. The patient received penicillin for one month and responded poorly. When streptomycin was also administered, there was dramatic improvement. This clinical experiment tends to substantiate Hewitt's work on animals, which demonstrated that streptomycin is much more effective than penicillin in saving guinea pigs inoculated with C. diphtheriae. In vitro tests with the organism isolated in this patient revealed evidence of neither synergism nor antagonism when studies were made with combinations of penicillin, streptomycin, sodium sulfadiazine and aureomycin. It is suggested that in future cases a combination of penicillin and streptomycin be used and sensitivity tests be performed on the organisms so that the physician may determine the proper dosage of antibiotic.

QUANTITATIVE METHOD FOR MEASURING H. PERTUSSIS ANTIBODY. Hattie E. ALEXANDER, CATHERINE MACPHERSON and WINIFRED REDMAN, Pediatrics **5**:443 (March) 1950.

A quantitative chemical method which determines the agglutinin nitrogen content is shown to be applicable to Hemophilus pertussis therapeutic antiserums.

The two human H. pertussis antiserums available for therapeutic purposes contain approximately the same agglutinin nitrogen content per vial, about 1 mg. A vial of the two rabbit antiserums analyzed contains approximately 20 mg. of agglutinin nitrogen.

A simple slide agglutination test is offered as a procedure for determining the degree of excess antibody in the serums of patient after serum therapy. The greater the content of agglutinin nitrogen in the therapeutic antiserum administered, the higher the relative agglutinin titer in the patient's serum.

STUDIES OF AN OUTBREAK OF POLIOMYELITIS IN IOWA WITH REFERENCE TO A FAMILIAL INCIDENCE AND THE PRESENCE OF VIRUS IN IMMEDIATE EXTRAHUMAN ENVIRONMENT. HERBERT A. WENNER and VERNON L. BRANSON, Pediatrics **5**:458 (March) 1950.

A study was made in a rural area of western Iowa to delineate the frequency of poliomyelitis in certain households and the presence of virus in extrahuman environment.

In certain families, poliomyelitis attacks many if not all members of the household but paralytic poliomyelitis does not develop in all members of the household. The onset of illnesses among members occurs at the same time, suggesting a common exposure. The factors responsible for an intense common exposure of most if not all members in a household at risk are largely unknown.

In a search for poliomyelitis virus in extrahuman sources in a rural epidemic, virus was detected in sewage and creek water. Poliomyelitis virus was not found in the entrails of birds, frogs or fish collected in the immediate areas of human cases of poliomyelitis.

EVALUATION OF THE MUMPS SKIN TEST. ALFRED L. FLORMAN, ALFRED E. FISCHER and RALPH E. MOLOSHOK, Pediatrics **5**:469 (March) 1950.

An intradermal test with formaldehyde-inactivated egg-grown mumps virus was done on 109 household contacts of 42 cases of mumps. Sixty of these persons showed positive reaction to a skin test and 49 negative. There were 12 contact cases of mumps, and 11 of them occurred among the nonreactors. There were 27 children who gave negative reactions to skin tests, and they furnished 10 of the contact cases. The possible significance of this fact is discussed.

The various types of reactions encountered are described and the frequent occurrence of relatively faint reactions in children noted. The validity of the test was supported by an obvious correlation with the incidence of secondary cases, past history and the fact that patients who originally showed negative reactions, showed positive reactions several months later.

It is concluded that the test is of value in determining susceptibility to mumps. In view of the large number of clinically inapparent cases, the skin test should prove most useful in practice in removing unnecessary concern about infection by parents who do not recall having had the disease.

THE USE OF FURMETHIDE (FURFURYL-TRIMETHYL-AMMONIUM IODIDE) FOR PARALYSIS OF THE BLADDER FROM POLIOMYELITIS. ROBERT B. LAWSON, South. M. J. **41**:251 (March) 1948.

A report is given on the use of furmethide® (furfuryl trimethylammonium iodide), a parasympathomimetic drug in the treatment of patients having paralysis of the bladder as a complication of poliomyelitis. Thirty patients were treated, chiefly by the subcutaneous route. The ages of the patients ranged from under 4 to 20 years; 18 patients were under the age of 14 years. Good results were obtained in 70 per cent of the entire group. Unpleasant side effects from other parasympathetic stimulation were observed infrequently and were counteracted by the use of atropine. The dose ranged from 1.25 to 2.5 mg. in the group under 4 years of age to 3 to 5 mg. in the group aged 15 to 19 years. The drug may be given orally in a somewhat larger dose. The author is of the opinion that furmethide® should be tried in the treatment of paralysis of the bladder in patients having poliomyelitis to avoid, if possible, the discomforts and hazards of catheterizations.

LOGAN, Rochester, Minn.

VACCINATION AGAINST WHOOPING COUGH AND DIPHTHERIA IN INFANCY AND EARLY CHILDHOOD. G. RAMON, R. DEBRÉ, M. LELONG, R. SOHIER and R. RICHOU, Presse méd. **56**:193 (March 20) 1948.

Whooping cough is the most serious infectious disease of early life and should be avoided by the use of preventive vaccine. Some of the sequelae of whooping cough are due to the endotoxin produced. The authors prepared a preventive mixture containing bacterial vaccine and toxoid. This was combined with diphtheria toxoid. The authors now are of the opinion that this mixture should be administered during the earlier months of infancy and are planning a large experimental program to test this thesis.

DAFFINEE, Melrose, Mass.

INFLUENCE OF POLIOMYELITIS ON THE PSYCHE. ERICH STERN, Ann. pædiat. **170**:280 (May) 1948.

The author describes the histories of 3 patients with character changes after poliomyelitis. The residual paralyses had created an inferiority complex, the normal compensation for which had not been achieved. The author emphasizes the necessity of psychotherapy as early as possible in patients of this kind.

FROM THE AUTHOR'S SUMMARY.

EPIDEMIOLOGIC, CLINICAL AND PATHOGENETIC ASPECTS OF EPIDEMIC OF MUMPS. B. GAGLIARDI, Pediat. d. med. prat. **23**:66 (March) 1948.

An epidemic of mumps occurred in Novara, Italy, with 482 cases reported between December 1946 and July 1947. Of 64 patients (aged 3 to 41 years) studied in the hospital for contagious diseases, 28 showed the characteristic spinal fluid

findings of mumps meningoencephalitis; 3 had meningitis without parotitis; 16 of the 28 showed no clinical meningeal symptoms. The meningitis was not commoner in the patients of any one age group or in any particular month of the epidemic. Orchitis was present in 2 of the men with meningitis. All the patients recovered. It appears that the contagium of mumps has a trophism for both the parotid glands and nerve tissue.

HIGGINS, Boston.

SERUM-ANATOXIN THERAPY IN DIPHTHERIA. A. VISANI, Pediatria. **56**:193 (April) 1948.

Ramon has recommended the following method of treating patients with diphtheria: the immediate injection of 0.1 cc. of diphtheria anatoxin (150 units per cubic centimeter); twenty minutes to one hour later the injection of diphtheria anatoxin in doses varying from 10,000 to 80,000 units according to the severity of the disease; forty-eight hours later an injection of 0.5 cc. of anatoxin, and at five day intervals further injections of 1, 2 and 3 cc. of anatoxin.

At the clinic for infectious diseases, in Rome, Italy, from December 1941 to February 1947, 3,365 children with diphtheria were treated according to this plan. There were 166 deaths (4.93 per cent); 390 children had complications. Of the 1,219 with the laryngeal form 260 required intubation or tracheotomy. Many of the deaths were from complications, the commonest of which was bronchopneumonia. The cases of the 30 children in whom the diphtheria recurred are individually reviewed. The opinion is expressed that the giving of anatoxin in the therapeutic plan contributes to a lessening of the number of recurrent attacks.

HIGGINS, Boston.

DOSAGE AND METHOD OF PROPHYLACTIC ADMINISTRATION OF DIPHTHERIA ANATOXIN. G. CADEDDU and A. SANNA, Pediatria **56**:245 (April) 1948.

An injection of 0.1 cc. of Ramon's anatoxin intracutaneously established and maintained a satisfactory antitoxic potency in the blood for one hundred and twenty days. None of the 52 children thus immunized had diphtheria over a four year period. A second similar injection given to the 30 per cent not protected by the first injection caused development of antitoxin in the patient. In practice it seems advisable to give the two injections.

HIGGINS, Boston.

RELATION OF CLIMATIC CONDITIONS TO MORBIDITY AND MORTALITY FROM DIPHTHERIA IN NAPLES, ITALY, FROM 1941 TO 1946. IRENE VERROTTI-CORTESE, Pediatria **56**:290 (April) 1948.

Diphtheria was at its lowest incidence in the summer and rose to its highest peak each autumn and winter with the fall in temperature. No definite relation between the morbidity or the mortality and the variations in the humidity, rainfall or barometric pressure could be determined.

HIGGINS, Boston.

LOCAL TREATMENT WITH PENICILLIN IN DIPHTHERIA CARRIERS. M. SCHACHTER, Policlinico inf. **16**:284 (June) 1948.

The author submitted to local treatment with a solution of penicillin several carriers of diphtheria bacteria and other patients who were cured but still carried the organisms. He obtained a negative culture within six days at the longest for all 63 persons treated.

FROM THE AUTHOR'S SUMMARY.

MENINGOCOCCIC MENINGITIS IN AN INFANT TREATED EXCLUSIVELY BY EXTRATHECAL ROUTE IN THE HOME, WITH RECOVERY. FERNANDO GASTELU, Arch. de pediat. d. Uruguay **21**:36 (Jan.) 1950.

An 8 month old infant was taken ill with meningococcic meningitis and was treated in the home with penicillin, streptomycin and sulfadiazine (the first two by the intramuscular route and the last by mouth) from the second day of disease. The course was rapidly favorable at thirty-six hours; the general and functional symptoms had disappeared totally, and spinal stiffness persisted a few more days. Recovery was without sequelae.

FROM THE AUTHOR'S SUMMARY.

PRELIMINARY REPORT ON TREATMENT OF WHOOPING COUGH WITH DISALBUMINIZED PANCREATIC EXTRACT. LEOPOLDO L. BENEDETTI, Bol. Asoc. med. nac. de Panama **12**:16 (Jan.) 1949.

Twenty-one patients with whooping cough treated with intramuscular injections of disalbuminized pancreatic extract with excellent results are reported on. The patients whose conditions were complicated by secondary infections of a light or medium intensity responded equally well to treatment with the disalbuminized pancreatic extract if the secondary infection was eliminated by penicillin or sulfonamide therapy.

FROM THE AUTHOR'S SUMMARY.

SHORT REVIEW OF THE RUBELLA PROBLEM. P. H. G. VAN GILSE, Bull. schweiz. Akad. d. med. Wissensch. **4**:89 (Sept.) 1948.

Rubella in women during the first months of pregnancy can give rise to a variety of congenital anomalies in children. A brief historical account is given, with the nomenclature and a discussion of various problems. Chiefly, the problems concern the character of this disease: its causes, the forms in which it appears and its diagnosis (plasma cells). The formation of antibodies is also involved. The associated problems of treatment and prophylaxis are discussed.

The question of the reason damage occurs to only the very young fetus and to only certain tissues or organs is raised.

Sociomedical consequences (including antepartum precautions, the responsibility of the family doctor, and medical officer, the health certificate and compulsory notification) are enumerated. The socioethical problem of "therapeutic abortion" is considered. So long as the agent, or the antibody, cannot be found or prepared outside the human body, the problems of organization consist in continual maintenance and holding in readiness of convalescent serum or convalescent gamma globulin (mixed "pooled" gamma globulin) for emergencies.

Problems are also raised by analogous poisoning due to other infectious diseases or even chemical agents. Experimentation on these problems is possible. The author reports on the previous work of a group of Dutch workers on rubella. He recommends closer international cooperation.

FROM THE AUTHOR'S ABSTRACT.

SCARLET FEVER: ITS COMPLICATIONS AND TREATMENT. I. ZIMÁNYI. Orvosok lapja **2**:1543 (Dec. 22) 1946.

Every child with scarlet fever brought to the hospital was given 1 mg. of thyroxin U. S. P. daily from the day of admission to the day of discharge. With the use of this treatment in 283 children, Zimányi observed that the complications (lymphadenitis, otitis and nephritis) occurred less often and their course was much milder than in the controls. Zimányi expresses his belief that the administration of thyroxin influences the disposition to complications most favorably.

GÖRGÉNYI-GÖTTICHE, Budapest, Hungary.

PROBLEMS IN THE PROPHYLAXIS OF INFECTIOUS DISEASES. F. FARAGÓ, Orvosok lapja **3**:249 (Feb. 23) 1947.

Preventive methods aim to give the body the most effective antigen with the longest possible action. The purified antigen leaves the body soon, but when it is adsorbed to protein or to aluminium hydroxide (Glenny, 1926) it has a satisfactory and lasting effect. Faragó used alum-precipitated diphtheria toxoid in Hungary first in 1933 and since then this method of protection has become compulsory. Hungary was the first state in Europe where prophylaxis against diphtheria was made compulsory.

The same procedure can be carried out with the toxin of scarlet fever. Faragó produced the first tannic acid–precipitated scarlet fever toxin in 1937. Its use resulted in an immunity rate of 90 to 95 per cent for three to four years. Even if children are protected against only the toxic effect and not the septic factors, this achievement is of great value.

It seems that even in the pathogenesis of whooping cough the toxic factor is of decisive importance. Faragó and Makara showed in 1942 that filtrates of Hemophilus pertussis can cause the same pathologic picture as the bacilli themselves show in experiments with white mice. In the prophylaxis of whooping cough probably the use of the toxin will play a determining role; therefore the elaboration of a practical method is urgently needed.

Concerning the influenza problem, at present it is known that the influenza virus originates from many different strains (influenza A and B and probably more) with different antigenic effects. Prophylactic measures against influenza have been begun and seem to show practical results.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

MODIFICATION OF RAPID CULTIVATION OF DIPHTHERIA BACILLI ACCORDING TO THE METHODS OF BRAHDY AND FOLGER. J. PÁLÓCZY, Orvosok lapja **3**:257 (March 2) 1947.

Pálóczy, active now as a physician in a country district of Hungary, uses the following method for rapid cultivation of diphtheria bacilli. A cotton wool swab in a glass tube placed in a baker's oven is sterilized at 160 C. If the tube is wrapped in newspaper, the browning of the newspaper will show that the temperature necessary for sterility has been reached. The sterile cotton wool swab then is dipped into human serum and put back into the tube. The tube should then be warmed to 60 C., or approximately as long as the unprotected hand can hold the tube. By this procedure the proteins of the human serum are coagulated and the immune substances are inactivated. The suspicious membranes in the throat should be touched with the swab and the swab immediately put back into the tube. The tube may be kept in the vest pocket, which serves as an incubator with a constant temperature of 35 C. After three to six hours smears from the swab may be microscopically examined.

Pálóczy, using this method, examined 26 cases, each of them reexamined by the Public Health Institute, and 24 showed the same result by the two examinations. Pálóczy obtained positive results in 2 cases in which the Public Health Institute failed. These 2 cases were clinically stated to be of diphtheria with subsequent paralysis. At this time communications were slow; therefore, the samples reached the distant Public Health Institute slowly. This modified Brahdy-Folger method means a great help for country physicians, for they can get results within a few hours, whereas the laboratory examinations take at least two to three days at present in Hungary.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

SCARLET FEVER AND NUTRITION. K. STOLL, Orvosok lapja **3**:396 (March 23) 1947.

The following table shows the morbidity, mortality and lethality rates of scarlet fever and measles in Budapest, Hungary, in the years 1914 to 1945:

	1914-1923			1924-1933			1934-1943			1944			1945		
	Per 100,000 Inhabitants		Lethality per 100 Persons	Per 100,000 Inhabitants		Lethality per 100 Persons	Per 100,000 Inhabitants		Lethality per 100 Persons	Per 100,000 Inhabitants		Lethality per 100 Persons	Per 100,000 Inhabitants		Lethality per 100 Persons
Disease	Morbidity	Mortality		Morbidity	Mortality		Morbidity	Mortality		Morbidity	Mortality		Morbidity	Mortality	
Scarlet fever	209.1	20.1	10.8	209.0	7.7	2.8	311.9	1.7	0.5	147.3	1.3	0.9	70.1	2.6	3.7
Measles	536.0	19.7	3.6	522.9	6.3	1.2	467.4	1.8	0.3	289.0	0.16	0.05	12.1	0.1	0.9

The morbidity rate of scarlet fever remained the same in the years 1914 to 1933. Later, a slight increase developed, i.e., in the years 1934 to 1943; whereas in the years 1944 to 1945, when Budapest suffered so much because of air attacks, the occupation and, finally, inflation, the number of cases of scarlet fever decreased rapidly, especially in 1945 when people lived in bunkers. The mortality rate did not decrease but increased slightly, because the incidence became a little worse than in 1934 to 1943. Stoll expresses his belief that the great decrease in morbidity rate was caused by the malnutrition, even starvation, of the population. Czerny made the same observation after World War I in Germany, where the incidence of scarlet fever showed the same decrease. In Budapest the number of cases of scarlet fever also diminished during 1918 to 1920, but not as in World War II. The same fluctuation may be observed in the case of measles. The mortality rate in 1945 was so low that only in 1919, after World War I, was such a small number observed.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

IMMUNITY TO MEASLES DEVELOPED IN INFANTS THROUGH INOCULATIONS. KAROLA PAPP, Paediat. danub. **3**:76 (Feb.) 1948.

One thousand eight hundred and two infants were inoculated, most of them three times, at the age of 5, 6½ and 8 months, respectively. Three thousand and twenty-two inoculations were given. Healthy infants suffered no damage from the inoculations. The reactions remained mostly below the threshold. Infrequently, a mild reaction occurred, with a rash and occasionally a slight elevation in temperature.

Many children could not be followed up. Those who could be found were reexamined in the spring of 1944 and the autumn of 1947, in both instances following epidemics of measles. Among the children who had been inoculated three times, the morbidity was 3 per cent in 1944 and 6.3 per cent in 1947. In no instances were complications observed. The percentage of mild measles-like infections was 18 and 19.2, respectively. Seventy-nine and 74.5 per cent resisted the infection until 1944 and 1947, i. e., they had not had the disease even eight to ten years after the inoculations.

FROM THE AUTHOR'S SUMMARY.

ACUTE ANTERIOR POLIOMYELITIS (HEINE-MEDIN DISEASE): A CLINICAL LECTURE. P. KISS, Paediat. danub. **3**:193 (April) 1948.

After a survey of the epidemiologic aspects, experimental data and history of poliomyelitis, the author calls attention to the fact that besides the specific lesions of the parenchyma edema of the mesenchyma occurs and this may lead to secondary changes after the granulocytic neuronophagia has come to an end. It is

supposed that an absolute or relative vitamin B_1 deficiency may also play a part in the sensitivity to infection and the lesions of the parenchyma. In spite of the negative reports, the prophylactic use of serum is advocated, together with large doses of vitamin B_1. The importance of hygienic measures and the avoidance of strenuous exercise, swimming, sports and traveling are stressed.

The various clinical forms of poliomyelitis are mentioned in detail and the cortical type described by Kiss and Fényes discussed. Contrary to the negative results reported, the therapeutic use of homologous serum and blood transfusions has proved of value in some cases and the author recommends their administration throughout the whole febrile period. To decrease the edema of the mesenchyma, 20 to 30 per cent solution of dextrose should be given intravenously, together with 100 mg. of vitamin B_1, two or three times a day. After the fever has ceased, roentgen irradiation of the spinal column may prove of value. From the third week onward, electrical treatment, massage, baths and diathermy are indicated.

FROM THE AUTHOR'S SUMMARY.

TREATMENT WITH STREPTOMYCIN IN THE DEPARTMENT FOR INFECTIOUS DISEASES IN THE BULOVKA HOSPITAL. B. LODROVÁ-ONDRÁCKOVÁ and A. TRAPLOVÁ, Pediat. listy **3**:11 (Jan.) 1948.

Streptomycin given in large amounts appears to have toxic effects. This the authors consider to be the explanation for the softening of and hemorrhages into the brain observed in 2 cases of tuberculous meningitis, and perhaps even for the convulsions and flaccid paresis of the left arm in a child with phlegmon of the thoracic wall. The application of smaller doses of this drug in tuberculous meningitis was successful in only 1 case, in which treatment is not yet finished. The best effect was achieved in a case of pneumonia caused by whooping cough and influenza. Less spectacular was the effect on hemolytic Escherichia coli in an infant with enteritis. It appears that treatment should start as early as possible, though according to some authors improvement is observed even when treatment is started some days after the onset of the disease. It cannot be denied that streptomycin stops the development of tuberculous meningitis and is an effective drug in chosen cases. It can be expected that as soon as greater experience is available the precise application and dosage will be ascertained.

FROM THE AUTHORS' SUMMARY.

THREE CASES OF PARALYSIS OF THE UPPER EXTREMITY AFTER DIPHTHERIA INOCULATION. KAREL POLACEK, Pediat. listy **3**:188, 1948.

Three cases are described of slight paralysis of the upper extremity which developed after diphtheria inoculation into the same arm. Two patients, members of the same family, showed nearly the same picture of the disease. After making a differential diagnosis, the author concluded that there are two possibilities: (1) acute poliomyelitis (Heine-Medin disease) which had been activated by the injection or introduced into the body, and/or (2) allergic polyradiculitis or myeloradiculitis on the basis of sensitivity of the organism to diphtheria anatoxin.

FROM THE AUTHOR'S SUMMARY.

MENINGOCOCCIC SEPSIS WITHOUT MENINGITIS. HELGE HÖJGAARD KRISTENSEN, Ugesk. f. læger. **109**:973 (Dec. 25) 1947.

In 1944-1945 the author treated 66 patients with evident meningococcic infection, of whom 27 had purulent meningitis and the rest, 39 patients, had signs of sepsis with petechial spots in the skin on admission. Among the latter patients

there were all degrees of pleocytosis of the spinal fluid, from absence of cells to purulence, with or without other signs of meningitis during the course of the illness.

WALLGREN, Stockholm, Sweden.

PENICILLIN TREATMENT OF SCARLET FEVER. A. FLAUM, Svenska läk.-tidning. **44**:1097 (May 16) 1947.

A report is made on the results of penicillin treatment in 240 patients with scarlet fever. As a control group the author chose 250 patients treated without penicillin one year previously. In the experimental series the penicillin was given intramuscularly in doses of 10,000 to 30,000 units six times daily, or 25,000 to 75,000 units three times daily, for seven days. If no hemolytic streptococci were recovered in three smears from the nose and throat, which was the case in 95 per cent, the patient was discharged. If the patient was not free from streptococci, the treatment was continued. The patients free from streptococci were, if possible, segregated from those with the organisms. A new bacteriologic study was made one week after discharge. Complications occurred in 5.4 per cent of the treated patients and in 45 per cent of the controls. The incidence of returned patients and relapses was no greater in the treated group. The author maintains that the economic gain for every penicillin-treated patient with scarlet fever is 164 Swedish crowns ($45).

WALLGREN, Stockholm, Sweden.

NEW RESEARCHES ON POSTVACCINAL ENCEPHALITIS AND REPORT OF A CASE OF POSTVACCINAL MYELITIS. P. K. KRAMER, Nederl. tijdschr. v. geneesk. **92**:3172 (Oct. 9) 1948.

A boy was vaccinated for the first time against smallpox at the age of 18 years. A week later he did not feel well, and two weeks after the vaccination the first symptoms of a myelitis appeared, resulting in paralysis of the lower extremities with complete anesthesia (only the deeper feeling was undisturbed), incontinence of feces and retention of urine. Further symptoms of meningitis were noted and the body temperature was increased. The cerebrospinal fluid was under a somewhat elevated pressure with slight pleocytosis (190 cells per 3 cu. mm.). The spinal column showed no abnormalities.

The temperature soon decreased; the neurologic symptoms diminished slowly but steadily. When discharged from the hospital, the patient still had a definite partial paralysis of the legs; he could walk with the aid of two canes. The sensorium was still distinctly disturbed, but with no complaints of involuntary micturition or defecation; the psychic condition was normal.

This patient shows, and it also is apparent from the literature, that the neurologic complication after vaccination is a meningomyeloencephalitis; however, the encephalitic and meningitic forms occur more frequently.

Based on the experiences of other investigators, Verlinde, of Leyden, Netherlands, succeeded in producing experimentally postvaccinal encephalitis in dogs by giving them injections of guanidine simultaneously with or previous to the vaccination. Guanidine is a product of the destruction of animal cell nuclei and is normally detoxified in the liver. When the liver is damaged or when guanidine is parenterally administered, this detoxification does not take place and the consequence is that the central nervous system becomes more sensitive to neurotropic viruses. By means of these experiments it could not be ascertained whether the encephalitis is caused by the vaccine virus or by an activated latent virus. Only once could a virus be demonstrated. These experiments probably explain the

reason that postvaccinal encephalitis so rarely occurs in children below the age of 1½ years. At that age they usually eat no meat. Therefore, it is perhaps advisable for the patient to eat no meat some weeks before and after the vaccination.

VAN CREVELD, Amsterdam, Netherlands.

WATERHOUSE-FRIDERICHSEN SYNDROME (EPIDEMIC CEREBROSPINAL MENINGITIS) SUCCESSFULLY TREATED WITH PENICILLIN AND SULFATHIAZOLE. HALVOR VERMUND, Tidsskr. norske lægefor. **67**:50 (Feb. 1) 1947.

A 16 month old boy became ill suddenly with a high fever and convulsions, and one day later purpuric spots appeared in the skin. When first seen, one and a half days later, he was ill with gray-bluish skin, somnolence, slight clinical signs of meningitis and purulent cerebrospinal fluid without any detectable bacteria. Penicillin was administered immediately, intrathecally for three days and intramuscularly for eight days (in all 530,000 units was given). Rapid improvement occurred and he was discharged from the hospital in a healthy condition on the twelfth day after his admission.

WALLGREN, Stockholm, Sweden.

PENICILLIN TREATMENT OF SCARLET FEVER. J. BÖE, Tidsskr. norske lægefor. **67**:419 (Aug. 15) 1947.

One hundred persons with mild scarlet fever were treated with intramuscular injections of penicillin eight times daily for at least six days, with a single dose of 2,000 units for children below 5 and of 30,000 units for children from 5 to 15 years of age. The treated children were segregated in rooms containing two or three beds, and patients who had been treated for one day were separated from the others. On the eighth day they were discharged from the hospital with one week of convalescent care at home. As early as the third day of treatment the hemolytic streptococci in 77 per cent of the children were no longer recovered in throat swabs. In 10 children there were mild complications, and in 1 child nephritis occurred.

WALLGREN, Stockholm, Sweden.

POLIOMYELITIS AFTER OPERATION ON THE NOSE AND THROAT. J. BÖE and ARNE KÅSS, Tidsskr. norske lægefor. **67**:485 (Sept. 15) 1947.

Of 526 patients with poliomyelitis (401 of whom were children below 15 years of age) treated from 1936 to 1945, manifestations of the bulbar type of the disease occurred two weeks after tonsillectomy in 1 child. This case occurred at a time poliomyelitis was not prevalent. In that part of Norway tonsillectomies and other minor operations in the upper respiratory tract are frequent. The authors consider the risk of acquiring poliomyelitis after such operations as almost negligible.

WALLGREN, Stockholm, Sweden.

EPIDEMIOLOGIC ASPECTS OF POLIOMYELITIS. ARNE K. HAUGETO and D. VIGELAND, Tidsskr. norske lægefor. **67**:607 (Nov. 15) 1947.

From observations in 21 cases of poliomyelitis occurring in a small Norwegian village and from examination of the milieu of the patients, the authors conclude that direct or indirect contact with the infected person primarily and with food and articles handled by him secondarily are the main factors in the spread of the disease. The epidemiologic measures in combating poliomyelitis should consider not only paralytic but also nonparalytic patients.

WALLGREN, Stockholm, Sweden.

Acute Infectious Diseases

THE FIRST TEN YEARS OF RHEUMATIC INFECTION IN CHILDHOOD. RACHEL ASH, Am. Heart J. **36**:89 (July) 1948.

The results of a follow-up study on 547 children who were observed for a ten year period following the onset of rheumatic infection are presented. At the termination of the initial attack, 59.2 per cent showed evidence of the presence of rheumatic heart disease.

Of 219 children with no clinical evidence of heart disease at the termination of their first attack, 76.7 per cent still showed no evidence of heart disease ten years after onset. Only 5 per cent of this group with potential heart disease at onset died of rheumatic infection or bacterial endocarditis.

Of 318 persons with rheumatic heart disease at onset, 30 (9.4 per cent) showed disappearance of the signs of cardiac involvement. Of this group with rheumatic heart disease at onset, 42.1 per cent died of rheumatic infection or bacterial endocarditis.

The most significant prognostic factor, so far as the initial illness is concerned, is related to the presence or absence of obvious signs of cardiac damage. Chorea at the onset is relatively benign because it is less likely to be associated with carditis than is polyarthritis or other types of rheumatic infection.

Ten years after onset, 60.3 per cent of these rheumatic persons were leading a normal existence, with little or no limitation of activity. The majority of patients presenting no functional incapacity, however, were those who showed no clinical evidence of heart disease at the termination of the initial attack. Twenty-four and four-tenths per cent of the total group died of rheumatic infection, the predominant number of deaths occurring among those for whom a diagnosis of rheumatic heart disease was made after recovery from the first attack. Death occurred in only 5 per cent of the group for whom an original diagnosis of potential heart disease was made, in comparison with a death rate of 42 per cent among those whose condition was diagnosed as rheumatic heart disease at onset.

FROM THE AUTHOR'S SUMMARY.

HEMORRHAGE IN DEEP INFECTIONS OF THE NECK. MAURICE D. GRANT and GOODLATTE B. GILMORE, Arch. Otolaryng. **47**:446 (April) 1948.

Deep infections in the neck usually extend along the layers of fascia and do not point outward. Such infections extend within the carotid sheath and erode an artery, causing sudden fatal hemorrhage. Two such cases are reported. Ligation of the internal and external carotid arteries is the treatment of choice in spite of the dangerous sequelae. If the internal carotid can be compressed in the neck for ten minutes without the development of symptoms (the Matos test), the artery can be ligated with safety.

KIMBALL, Evanston, Ill.

THE ELECTROCARDIOGRAM IN RHEUMATIC FEVER. JULIUS KAHN, EDWARD SHAPIRO and MAURICE L. LIPKIS, California Med. **69**:449 (Dec.) 1948.

The electrocardiographic changes of rheumatic fever are not specific for this disease. The change of greatest frequency is prolongation of the P-R interval, which may occur in varying degrees up to complete dissociation of auricle and ventricle. After the teaching of Cohn and Swift, an increase of over 0.02 second in the P-R interval should be considered significant. Changes in the P-R interval can occur in either the acute or the subsiding stage of the disease. Only in rare

cases does this change persist with quiescence. Changes in the ventricular portion of the electrocardiogram are also important. Gross changes in the QRS segment are significant, as is an absent R wave in lead IV. Prominent elevation or depression of the S-T segment and depressions of the T wave are significant, especially when the two are combined. All these changes are of added significance if it can be shown that they are deviations from the patient's normal tracing. Auricular fibrillation is the most significant of the arrhythmias that can occur during the course of rheumatic fever. Other disturbances of rhythm, those involving the auriculoventricular node possibly being of greater importance, are not infrequently noted.

Not all patients with rheumatic carditis, even when the disease is severe, show electrocardiographic changes; pronounced electrocardiographic changes can occur without clinical evidence of disease.

PRYOR, Redwood City, Calif.

A PRELIMINARY REPORT OF RHEUMATIC FEVER IN VIRGINIA. C. M. McCUE and T. F. GALVIN, J. Pediat. **33**:467 (Oct.) 1948.

The results of a study on rheumatic fever which has been in progress for seven years in the state of Virginia are reported. Observations are compared with the published data from other series of cases. The authors point out the relatively short period of their study with respect to interpretation of mortality and other statistics. In other respects, this carefully analyzed project does not lend itself to abstraction.

C. G. GRULEE JR., Galveston, Texas.

CLINICAL FEATURES OF A SUMMER DISEASE (THREE-DAY FEVER). C. H. WEBB, S. GEORGE WOLFE and VERRE SIMPSON, New Orleans M. & S. J. **101**:249 (Dec.) 1948.

The authors present a study of 40 patients with a condition they call "three day fever." The patients all presented a picture of sudden onset of fever, headache, often myalgia, and absence of notable involvement of respiratory or gastrointestinal tracts. Recovery was as prompt as the onset, and no treatment influenced the course of the disease. Laboratory work failed to demonstrate a bacterial cause. The disease is considered to be of virus origin.

McGUIGAN, Evanston, Ill.

CONSIDERATION OF MANAGEMENT OF CHILD WITH RHEUMATIC FEVER. ARILD E. HANSEN, New Orleans M. & S. J. **101**:264 (Dec.) 1948.

Hansen presents a detailed discussion of the management of the child with rheumatic fever in all its phases, with particular emphasis on the need for close supervision during the quiescent stage. He considers that such supervision should be carried on until after the child has reached puberty.

McGUIGAN, Evanston, Ill.

IMMUNOLOGIC AND BIOCHEMICAL STUDIES IN INFANTS AND CHILDREN WITH SPECIAL REFERENCE TO RHEUMATIC FEVER: IV. OCCURRENCE OF AGGLUTININS IN NORMAL AND ABNORMAL CONDITIONS. PAUL F. DEGARA, Pediatrics **2**:410 (Oct.) 1948.

Agglutinins for three strains of group A beta hemolytic streptococci were studied in 497 serums from 372 children. A high titer was detected in approximately 46 per cent of the children who had had infections presumably streptococcic

in origin. In those with active rheumatic fever, high titers were present in 9 of 11 patients who had experienced an antecedent infection, presumably streptococcic in origin. Of 23 rheumatic patients with no history of antecedent illness, only 3 had high titers of streptococcic agglutinins.

FROM THE AUTHOR'S SUMMARY.

IMMUNOLOGIC AND BIOCHEMICAL STUDIES IN INFANTS AND CHILDREN WITH SPECIAL REFERENCE TO RHEUMATIC FEVER: V. ELECTROPHORETIC PATTERNS IN BLOOD PLASMA AND SERUM IN NORMAL CHILDREN. ROSE LUBSCHEZ, Pediatrics **2**:570 (Nov.) 1948.

Electrophoretic patterns in blood plasma and serums were determined for 59 normal children in apparent health from under 1 year to 11 years of age. Possible influences of heredity, age, sex and antecedent illness were considered. Determinations were made by the published method in the Tiselius-Longsworth apparatus, with the use of a barbiturate buffer.

Electrophoretic analyses of blood plasma or serum of 30 children in apparent health between 2 and 11 years old revealed that the relative concentration of the various components agreed closely with adult values, although individual variation was several times greater.

For 27 children who were in apparent health, but had had various types of infection during a one to four month interval prior to the time the specimen was taken, elevation of the gamma component occurred in about 40 per cent of the determinations. Illness within the month produced the greatest number of abnormalities, although abnormalities were noted in specimens from children who had been free of infection two to three months. A few abnormalities were noted in all components except beta globulin.

At younger ages (2 to 4 years), children showed a slightly higher albumin level and a slightly lower gamma globulin level. Normal children susceptible to rheumatic fever on a genetic basis exhibited no specific differences in the electrophoretic pattern.

FROM THE AUTHOR'S SUMMARY.

IMMUNOLOGIC AND BIOCHEMICAL STUDIES IN INFANTS AND CHILDREN WITH SPECIAL REFERENCE TO RHEUMATIC FEVER: VI. ELECTROPHORETIC PATTERNS OF BLOOD PLASMA AND SERUM IN RHEUMATIC CHILDREN. MAY G. WILSON and ROSE LUBSCHEZ, Pediatrics **2**:577 (Nov.) 1948.

A correlation of the change in the electrophoretic pattern of plasma and serums in persons with rheumatic fever is presented. Electrophoretic analyses are presented for 79 specimens of blood plasma or serum from 42 rheumatic subjects during apparent health, after respiratory illness and during rheumatic fever. Electrophoretic studies revealed a prolonged elevation in the gamma component for a period varying from weeks to months following an antecedent respiratory illness with or without the development of rheumatic fever. During acute rheumatic fever, the gamma globulin component was normal in the absence of antecedent illness. Elevation of the gamma globulin component in rheumatic fever is not a function of the rheumatic process. The alpha globulin components were usually elevated during febrile periods. No evidence was obtained in these studies that the immune response of rheumatic subjects to infections presumably streptococcic in origin differed from that of nonrheumatic persons.

FROM THE AUTHORS' SUMMARY.

RHEUMATIC PNEUMONITIS IN CHILDHOOD. HAROLD B. LEVY, JOHN D. COFFEY and CHARLES E. ANDERSON JR., Pediatrics **2**:688 (Dec.) 1948.

Awareness of the manifestations of rheumatic fever in organ systems other than the cardiovascular is essential. In the lungs there has been observed a characteristic diffuse interstitial pneumonitis, which often appears sufficiently severe to be considered a major contributing factor to, if not the actual primary cause of, death.

Microscopic examination reveals four types of lesions: granuloma (or Masson body), focal fibrinoid necrosis and alveolitis with hyaline membrane formation, arteriolitis and septal cell proliferation.

Six cases of acute rheumatic fever, with severe pulmonary involvement, are presented with clinical and pathologic data. The patients were Negroes, varying in age from 2½ to 8 years. The clinical course of each was that of a severe and rapidly fatal infection. Therapeutic efforts were of no avail.

FROM THE AUTHORS' SUMMARY.

CHLOROMYCETIN IN THE TREATMENT OF PATIENTS WITH TYPHUS FEVER. JOSEPH E. SMADEL, ALBERT P. LEÓN, HERBERT L. LEY JR. and GERARDO VARELA, Proc. Soc. Exper. Biol. & Med. **68**:12 (May) 1948.

Three adults and 2 children were given crystalline chloromycetin by mouth in the treatment of typhus fever (both murine and epidemic), with apparently favorable results.

HANSEN, Galveston, Texas.

AN EPIDEMIC OF GLANDULAR FEVER. F. R. BUCKLER, Arch. Dis. Childhood **23**:92 (June) 1948.

An epidemic of infectious mononucleosis was described which occurred in a closed community. The first 2 cases were severe and showed parotid involvement; the succeeding cases were less severe, and the epidemic died out in three months.

There was only a slight mononucleosis in the first weeks of the disease, which rapidly disappeared. An eosinophilia appeared early and gradually increased for a period up to three months. There was a secondary anemia. All Paul Bunnell titrations showed no heterophil antibodies. There was no splenic enlargement.

KELLY, Milwaukee.

THE NUTRITIONAL STATE OF CHILDREN WITH CHRONIC RHEUMATIC HEART DISEASE. JOSEPH BENN, Arch. Dis. Childhood **23**:175 (Sept.) 1948.

Rheumatic heart disease probably has no inhibiting effect on the growth of children, once the infection has subsided. The type of rheumatic infection and the presence of cardiac enlargement are also without effect.

KELLY, Milwaukee.

TREATMENT OF TAPE WORMS WITH ATABRINE. A. HALAWANI, I. BAZ, A. HAFEZ and M. K. SHAWARBI, J. Roy. Egyptian M. A. **31**:956 (Dec.) 1948.

Quinacrine hydrochloride (atabrine® di-hydrochloride) gave good results as a vermifuge. No summary or analysis of results is given. The drug does not appear to be successful in eradication of round worms.

MCGUIGAN, Evanston, Ill.

THE INTENSIVE TREATMENT OF SCHISTOSOMIASIS WITH TARTAR EMETIC. S. M. TALAAT and S. SHOAIB, J. Roy. Egyptian M. A. **31**:961 (Dec.) 1948.

Eighty per cent of the patients with schistosomiasis were cured by two injections of antimony potassium tartrate (tartar emetic) daily for two days. Children under 15 years of age required an extra dose on the third day.

McGUIGAN, Evanston, Ill.

TOXOPLASMOSIS: REPORT OF A CASE WITH RECOVERY. P. ROBINSON, Ann. paediat. **168**:134 (March) 1947.

A girl 9 years of age became acutely ill. After fourteen days of high fever, neurologic symptoms became evident. Strabismus, nystagmus and chorioretinitis were present. Abdominal reflexes were absent. The Kernig and Babinski signs were elicited, while knee and ankle jerks were absent. It is probable that the chorioretinitis would have been discovered sooner had a funduscopic examination been made.

The first lumbar puncture revealed normal fluid which already contained Toxoplasma parasites. The fluid of the second and third lumbar puncture coagulated immediately, and it also contained encysted and free Toxoplasma parasites. After clinical recovery, the cerebrospinal fluid became normal.

Treatment with sulfathiazole, 0.75 Gm. every four hours, and emetine, 0.015 Gm. daily, continued for twelve days, resulted in clinical recovery. However, nine days after treatment was discontinued, the temperature rose again and some of the neurologic symptoms reappeared. The treatment was resumed and continued for six more days, after which the child made a complete and final recovery.

FROM THE AUTHOR'S ABSTRACT.

HEMORRHAGIC INFARCTION OF THE TESTICLE IN STRANGULATED INGUINAL HERNIA IN INFANCY. ORESTE MAZZARELLA, Arch. ital. pediat. e puericolt. **11**:333, 1946.

Hemorrhagic infarct of the testicle in a strangulated inguinal hernia of infancy is a condition recorded in the literature in only *2* surely established cases. Three personal cases are referred to, one with histologic observations. The term proposed by the author, "funicular herniary strangulation," is better related to the clinical syndrome and its anatomic manifestations. After reviewing different types of testicular infarctions and atrophies, the author draws the conclusion that the involvement of the spermatic cord by a strangulated inguinal hernia is one of the most frequent causes of spontaneous infarction of the testicle and is perhaps the only cause of the hemorrhagic infarction in infancy. The medicolegal aspects of funicular herniary strangulation and the necessity of evaluating its importance as to the prognosis and earliness of surgical treatment are discussed.

FROM THE AUTHOR'S SUMMARY.

CLINICAL OBSERVATIONS IN TEN CASES OF PNEUMOCOCCIC MENINGITIS. S. FOLENA, Clin. pediat. **30**:618 (Oct.) 1948.

The accentuation of cranial tympany on percussion is stressed as being an early and valuable diagnostic finding in cases of pneumococcic meningitis. The sign may represent an early blockage of the foramens between the ventricles and the subarachnoid space.

HIGGINS, Boston.

MENINGOENCEPHALITIC COMPLICATIONS IN TYPHOID AND PARATYPHOID. ALFREDO AGNESE, Policlinico inf. **16**:134 (March) 1948.

The author, after briefly mentioning the difficulties of classifying the meningoencephalitic complications of typhoid and paratyphoid, describes several cases he has studied of the diseases in children.

FROM THE AUTHOR'S SUMMARY.

RESEARCHES ON GENESIS OF MICROERYTHROBLASTOSIS: II. ERYTHROBLASTOSIS IN CHILDHOOD LEISHMANIASIS. GIOVANNI ASTALDI, VITTORIO GALLO and PAOLO TOLENTINO, Policlinico inf. (supp.) **16**:44 (Jan.) 1948.

The authors, continuing their studies on the genesis of the microerythroblastosis of familial erythroblastic anemia (Cooley) and in order to exclude the possible genetic influence of extramyeloid conditions on the microerythroblastosis they demonstrated in this disease, performed erythroblastometric studies in 5 cases of infantile leishmaniasis, a disease in which a medullary erythroblastosis occurs, secondary to peripheral hyperhemolysis. It has been demonstrated in these studies that a microerythroblastosis also exists in infantile leishmaniasis; in contrast to the microerythroblastosis of familial erythroblastic anemia (which involves all erythroblasts, basophils, polychromatophils and orthochromatic cells), it is limited to the orthochromatic elements. From the comparison of serial studies it appears furthermore that in some cases of leishmaniasis the nuclear diameter is distributed in a bimodal fashion as in normal blood, a trait that is not observed in familial erythroblastic anemia.

These results, justifying the authors' previously expressed caution in regard to the interpretation of the microerythroblastosis of familial erythroblastic anemia, show at any rate the existence of several differences between the two diseases; these differences could be the expressions of a different pathogenetic mechanism (secondary in leishmaniasis, primary in familial erythroblastic anemia) or even of a common hemolytic noxa, more chronic and of an older date in familial erythroblastic anemia than in leishmaniasis, so that it may have influenced even the polychromatophil and orthochromatic elements.

FROM THE AUTHORS' SUMMARY.

PENICILLIN THERAPY IN AMBULATORY TREATMENT OF GONORRHEAL INFECTIONS IN CHILDREN. ALFREDO WIEDERHOLD and ANTONIETA MENDEZ, Arch. de pediat. de Uruguay **18**:576 (Nov.) 1947.

In a previous paper, the authors reported the results of the ambulatory treatment of gonococcic infections in the child with penicillin by the oral route. Of 25 children treated in this manner over a period of more than six months and submitted to an intense reactivation with protargol* and neogynergen,* (a tablet containing ergotamine tartrate and ergonovine tartrate), all were cured bacteriologically and clinically. They also demonstrated that penicillin administered by the oral route is eliminated in sufficient amount and rapidly enough that maintenance of a constant and uniform penicillin level in the blood is not necessary. Small and repeated discharges of the drug through the urine are all that is needed to destroy the gonococcus. This is an easy treatment, giving favorable results; its simplicity and the possibility of maintaining secrecy are sufficient to make it worthy of being known. Most of the children were treated with doses of 300,000 to 600,000 units.

Administration of penicillin by the intramuscular route requires smaller doses (100,000 to 250,000 units); some children were not cured with this, and it was

necessary to employ new dosage levels by the oral route. After a bacteriologic examination of the discharges from the urethra or the vulva and vagina, the children still showing organisms were treated usually with 100,000 units, with increasing doses for those in whom the secretion persisted and the slides continued being positive.

A suspension of common sodium penicillin was used, 100,000 units in 2 cc. of sterile olive oil. Of this group of 26 patients, 21 recovered clinically and bacteriologically; the other 5 maintained the purulent discharges and the presence of gonococci on the slides; as they did not recover with the increase in the dose, the oral route was used, resulting in a complete recovery. As a test of recovery the reactivation of the gonococcic infection by instillations of a 10 per cent solution of protargol® or of neogynergen® was used. Of the patients treated with penicillin by oral route, none had a relapse.

FROM THE AUTHORS' SUMMARY.

AMEBIC DYSENTERY IN CHILDREN. G. CARDELLE and J. C. SÁENZ, Pediat. Américas **6**:14 (Jan.) 1948.

In Cuba amebic dysentery is less frequent than bacillary dysentery. Amebic dysentery is not exceptional in children under 6 years of age, but in this group hepatic abscess is rare. In small children the illness has a more acute symptomatology than in older patients. The treatment proposed consists in administration of emetine during the acute period (0.75 to 1 mg. per kilogram of body weight per day), followed by therapy with one of the arsenicals or oxyquinoline.

Before a patient can be declared cured he must have two negative parasitoscopic studies made in the two months after cessation of clinical signs. It is highly desirable to have also a proctoscopic examination with normal results.

DE LA TORRE, México, D.F., Mexico.

TYPHUS IN CHILDREN. R. POUS ROCA, Pediat. Américas **6**:98 (Feb.) 1948.

The author reports 46 cases studied from 1943 to 1947. Twenty were of children over 10 years of age, 17 of children between 6 and 10 years old and 9 of younger patients. Only 1 died.

The main symptoms were fever that lasted in the majority of the patients fifteen days or more and was high and sustained, conjunctivitis, pharyngitis and tachycardia, low blood pressure in 13 children, bronchitis and bronchopneumonia in 10, enlarged liver in 12 and enlarged spleen in 24; meningoencephalitic symptoms accompanied with high proteins and increased cell count in the spinal fluid appeared in 12 patients. There was no rash in 21 of them.

The Weil-Felix reaction was positive in all 46 patients; in 26 the titers varied from 1:1,280 to 1:20,280. Studies with the specific antigens and complement fixation reaction done on 26 of the children showed that 22 had epidemic typhus and 4 murine typhus. No specific therapy was employed.

DE LA TORRE, México, D.F., Mexico.

INFECTIOUS LYMPHOCYTOSIS. J. HOUSTEK, Pediat. listy **3**:21 (Jan.) 1948.

Two typical cases of the disease are described in a boy 2 years of age and his sister 6 years old. In the first child the history revealed drowsiness, somnolence and abdominal pain. In the second the diagnosis was established only on the basis of the hematologic findings. The leukocyte count in the girl was 71,800, with 90 per cent lymphocytes. Sternal puncture revealed 74.7 per cent lymphocytes. The white blood cell count in the boy gave a value of 24,200, with 91 per cent lymphocytes. Lymphatic reactions are common in childhood and both infectious mono-

nucleosis and infectious lymphocytosis were differentiated from them as separate entities. In Czechoslovakia both are less frequent than in England and America. Infectious lymphocytosis occurred before 1940, but it was listed among the atypical cases of infectious mononucleosis. The diagnosis has practical value in the differential diagnosis of transient erythema and because it may draw attention to the occurrence of similar cases in the vicinity.

FROM THE AUTHOR'S SUMMARY.

SLIDE AGGLUTINATION TEST FOR RAPID DIAGNOSIS OF TYPHUS AND TYPHOID FEVERS. N. C. CHANG, Chinese M. J. **66**:612 (Nov.) 1948.

This simple slide agglutination test for typhus and typhoid compared favorably in accuracy with the classic tube agglutination method. Antigens prepared from Bacillus proteus O X_{19} and Ebefthella typhosa O_{901} were used. (H_{901} antigen was not used because it sometimes gave high titers.) A drop of antigen placed on a glass slide is mixed with a drop of undiluted serum in this test. The slide is then tilted back and forth rapidly for one minute and the mixture then examined with the naked eye for clumping. If this occurs, the test is repeated using serum diluted with an equal amount of isotonic sodium chloride solution. In this manner, twofold serial dilutions of serum may be tested until a negative reaction is reached. Reactions that occur at a dilution of 1:4 or higher are considered significant for typhus or typhoid.

MACDONALD, Pittsburgh.

Chronic Infectious Diseases

TUBERCULOUS MENINGITIS IN CHILDREN WITH SPECIAL REFERENCE TO SEROUS MENINGITIS: I. TUBERCULOUS MENINGITIS. EDITH M. LINCOLN, Am. Rev. Tuberc. **56**:75 (Aug.) 1947.

The stated purpose of these papers is to analyze a series of 167 cases of meningitis and to differentiate tuberculous meningitis from a clinical picture occurring not infrequently in children which may be termed serous tuberculous meningitis, a less serious and less deadly form of the disease.

The differentiation of an almost certainly fatal manifestation of tuberculosis from a less serious one is especially important in assessing the value of the newer chemotherapeutic agents in the treatment of the disease.

The clinical progress of tuberculous meningitis may be divided into three stages. During the first stage gastrointestinal rather than neurologic symptoms predominate. The child may show unexplained irritability or, on the other hand, may be apathetic. Occasionally, convulsions may occur in children under 2 years of age. During the second stage, the child becomes stuporous and such neurologic signs as hyperactive deep reflexes, diminished abdominal reflexes, positive Kernig and Brudzinski signs and ankle and patellar clonus may appear, usually transient at first. Evidence of involvement of the cranial nerves, usually strabismus, ptosis, nystagmus or paralysis of the facial nerve, may appear during this stage. Fixed or unequal pupils, clonic spasms of the extremities and meningitic (Biot type) respiration may occur during this stage, but usually not until later. The final stage is usually one of steadily increasing stupor. There is almost invariably some degree of nuchal rigidity, combined with positive Kernig and Brudzinski signs.

Especially in those children not known to have tuberculosis examination of the spinal fluid is the only means of confirming the diagnosis. Tubercle bacilli may or may not be found. A low or falling sugar level is the most important finding. A clear fluid, with high protein, low sugar and low chloride content and moderate

pleocytosis, practically confirms a clinical diagnosis of tuberculous meningitis, especially if there is pellicle formation on standing. Anergy to tuberculin is relatively uncommon, even in well developed attacks of meningitis, since 85 per cent of the patients tested gave positive cutaneous reactions.

SMITH, Ogden, Utah.

TUBERCULOUS MENINGITIS IN CHILDREN: II. SEROUS TUBERCULOUS MENINGITIS. EDITH M. LINCOLN, Am. Rev. Tuberc. **56**:95 (Aug.) 1947.

Part I of this study dealt with a type of tuberculous meningitis which was invariably fatal. Another but smaller group of patients was observed with physical signs and symptoms suggestive of tuberculous meningitis; some of these apparently recovered completely. The disease in this group the author terms serous tuberculous meningitis, a condition which in her opinion is due either to the perifocal reaction around seedlings in the early primary or postprimary stages or to later collateral inflammation around older caseous foci in the cortex or meninges.

The clinical pictures of these two types of disease may be similar, especially in the early stages. Vomiting, drowsiness or apathy, with sudden elevation in temperature and irritability, are common in both conditions. The signs of meningeal irritation, stiff neck and positive Kernig and Brudzinski signs, may also be present. Prominent early general symptoms with few neurologic signs would suggest the possibility of serous meningitis. Ankle clonus associated with nuchal rigidity are commonly found, with occasional involvement of the cranial nerves. The deciding factor in differential diagnosis in most cases is the spinal fluid findings. In serous meningitis there may be an increase in pressure and number in cells, but the chemical content, sugar, protein and chloride levels remains normal. Even the presence of a few acid-fast bacilli is not incompatible with the diagnosis of serous meningitis.

Twelve cases of serous meningitis are described, all occurring in children with active pulmonary tuberculosis. Three of the children were well eleven to fifteen years later. Four died without further evidence of meningeal involvement, four to thirty-two months after recovery from serous meningitis. Signs of meningeal irritation persisted until death in 4. In 1 child a brief remission of symptoms was followed by death from tuberculous meningitis.

SMITH, Ogden, Utah.

TOXOPLASMOSIS. PAUL KABLER and MARION COONEY, Minnesota Med. **30**:637 (June) 1947.

Typical toxoplasmosis occurring in a 14 year old female resident of Minnesota was reported by Adams, Horns and Eklund in 1946. Since that time, the authors have begun neutralization tests for the Toxoplasma organisms on patients scattered throughout the state. The technic of the tests is essentially that described by Sabin, in which patients' blood serums are mixed with suspensions of the organism and inoculated into the skin of white rabbits.

These tests show that toxoplasmic infections are probably widespread in Minnesota in that the neutralizing antibodies were present in the blood of persons who came from twenty-five counties. Checking back on the cases, the authors learned that toxoplasmosis may occur in utero or may be acquired at any age. Infantile toxoplasmosis is usually characterized by widespread destruction of the central nervous system, and, in surviving children, residuals, such as hydrocephalus, convulsions, chorioretinitis and mental retardation, are frequent.

STOESSER, Minneapolis.

STREPTOMYCIN IN CHILDHOOD TUBERCULOSIS. GLADYS L. BOYD, Canad. M. A. J. **60**:476 (May) 1949.

The use of streptomycin in tuberculosis is discussed. The most satisfactory results were in patients with the pulmonary disease, all of whom remained cured after two years. Its use in other forms of tuberculosis is encourging, but better results may be obtained by more careful selection of cases, especially in tuberculous meningitis.

MCGUIGAN, Evanston, Ill.

PRIMARY TUBERCULOUS INFECTION IN CHILDHOOD: INCIDENCE, MORBIDITY, AND MORTALITY IN AN URBAN POPULATION. BRIAN C. THOMPSON, Arch. Dis. Childhood **22**:1 (March) 1947.

In the absence of large scale tuberculin testing of true population samples, selected groups studied at the Ealing Chest Clinic, London, England, give some guide to the incidence of tuberculous infection at various ages in childhood for the population concerned. The patch test has proved a reliable index of a relatively high degree of sensitivity to tuberculin. Results of epidemiologic value, however, require the use of intradermal tests equal to at least 1 to 100 old tuberculin in children with negative reactions to the patch test. The patch test alone will detect sensitivity in most persons with active tuberculosis with manifest lesions. Routine examination of children known to have been in contact with persons with tuberculosis will reveal active tuberculosis in a proportion at least as high as that found in children who are not known contacts but who have symptoms. The highest incidence of manifest lesions is found in children at the time of conversion from a negative to a positive tuberculin reaction. Negative reactors should, therefore, be repeatedly retested as long as the risk of infection continues.

KELLY, Milwaukee.

PREPARATIONS OF B.C.G. VACCINE AND THE TECHNIQUE OF ITS ADMINISTRATION. P. K. CHATTERJEE, Indian J. Pediat. **16**:6 (Jan.) 1949.

The preparation of BCG vaccine is briefly summarized. The various technics of vaccination are described. The intracutaneous method is preferred.

MCGUIGAN, Evanston, Ill.

CONTROL OF TUBERCULOSIS: THE ROLE OF BCG AND VOLE VACCINES, WITH PARTICULAR REFERENCE TO THE NON-EUROPEAN POPULATION OF SOUTH AFRICA. B. A. DORMER, South African M. J. **23**:488 (June 18) 1949.

A program for tuberculosis control among South African natives is suggested. The program would involve the usual hygienic measures, plus wide scale tuberculin testing and the giving of BCG or vole vaccine to negative reactors. The basis for the advocacy of vole vaccination is not clear, since the author devotes only some ten lines to a discussion of this vaccine and concludes by remarking that it has been used experimentally in a few cases in man.

MCGUIGAN, Evanston, Ill.

USE OF TOMOGRAPHY IN EVALUATION OF PULMONARY TUBERCULOSIS. F. ROTACH, Helvet. paediat. acta **3**:23 (Feb.) 1948.

In many cases of pulmonary tuberculosis occurring in children tomography alone is sufficient to demonstrate the presence or absence of a cavity, especially incipient central tissue destruction within a thick infiltrate. In the case of a

primary tuberculous focus, often a correct qualitative estimation is possible only by this means. From the proof in the tomogram of incipient tissue destruction on the one hand and of incipient calcification on the other, the developmental tendency of the focus can be recognized at an early date. For the tomographic diagnosis of hilar node tuberculosis, knowledge of the anatomic conditions of the hilar region is indispensable to a correct interpretation. In general, smaller nodular swellings cannot be ascertained with certainty in the tomogram. The form and position of tumorous nodular enlargements can be ascertained with greater accuracy. In individual cases larger tuberculous nodes are demonstrated in the tomogram when no definite nodular shadows are discernible in an ordinary roentgenogram. Important groups of nodes, especially on the left side, escape diagnosis even by tomography. In epituberculosis, which may be due to perifocal infiltration or to resorptive atelectasis following compression of a larger bronchus, the occlusion of the bronchus demonstrates as the only sure roentgenologic smyptom the presence of a resorptive atelectasis.

FROM THE AUTHOR'S SUMMARY.

DISSEMINATED TUBERCULOSIS IN AN INFANT FOLLOWING PROPHYLACTIC VACCINATION WITH PETRAGNANI-SALVIOLI TUBERCULIN. C. CORONA, Clin. pediat. **30**:177 (March) 1948.

The Petragnani-Salvioli vaccine contains tubercle bacilli killed by formaldehyde. The patient had been vaccinated shortly after birth. She became ill at 2 months of age and died two months later of miliary tuberculosis, with a primary focus in the right lung.

HIGGINS, Boston.

ALLERGOMETRY OF VON GROER AND ERYTHROCYTE SEDIMENTATION RATE IN MILIARY AND MENINGEAL TUBERCULOSIS TREATED WITH STREPTOMYCIN. L. MARTONI, Clin. pediat. **30**:319 (May) 1948.

Von Groer's test involves the measurement of the amount of reaction following intradermal injections of 1 to 10,000 and 1 to 1,000,000 dilutions of tuberculin. Of 29 patients with miliary or with meningeal tuberculosis under treatment with streptomycin, 4 showed anergy, 8 a slight reaction to tuberculin and 17 a pronounced reaction. Repetition of the tests showed a tendency for the anergic patients to become allergic. There were 7 deaths among the 29, proportionally divided among the three groups.

HIGGINS, Boston.

NEED OF AN ANTITUBERCULOSIS CAMPAIGN IN VIEW OF THE MORBIDITY AND MORTALITY STATISTICS SINCE THE WAR. S. BARBERI and A. FERLAZZO, Clin. Pediat. **30**:605 (Oct.) 1948.

In Italy, there was an average of 38 deaths due to tuberculosis per million inhabitants per year during the decade of 1930 to 1940. In 1946 there were 500 deaths from tuberculosis per million inhabitants.

In the pediatric clinic at Messina, the incidence of tuberculosis among its patients continues to remain high three years after the war, especially in children under 2 years of age and that of the miliary and meningeal types.

A campaign for education and proper care should be instituted under a single and independent unit to combat the ravages of this disease.

HIGGINS, Boston.

TUBERCULOUS MENINGITIS TREATED WITH STREPTOMYCIN WITH A FATAL OUTCOME. ROLANDO BULGARELLI and ANTONIO GIAMPALMO, Policlinico inf. **16**:49 (Feb.) 1948.

The authors present a histopathologic study of the alterations in the meninges and brain of 5 children with tuberculous meningitis who were treated with streptomycin. Special attention is given to the relationships between the clinical and the pathologic pictures.

FROM THE AUTHORS' SUMMARY.

CRANIAL LESIONS OF A DESTRUCTIVE TYPE IN CONGENITAL SYPHILIS OF EARLY INFANCY. ROLANDO BULGARELLI and ALFREDO DE MAESTRI, Policlinico inf. **16**:149 (April) 1948.

The authors noted with great frequency destructive changes on roentgenograms of the skull in syphilitic infants under 1 year of age. They point out that the study of these cranial alterations in early infancy has been too much neglected because the prevailing concept emphasizes that such destructive alterations are usually met only in children over 2 years of age. They also point out that the frequent finding of these changes, even in early infancy, demonstrates the lack of clear-cut limits among the various stages of congenital syphilis.

FROM THE AUTHORS' SUMMARY.

LOBAR AND SEGMENTAL LOCALIZATION OF TUBERCULOSIS IN CHILDREN. TEODOSIO VALLEDOR, Rev. cubana de pediat. **19**:189 (April) 1947.

When compression is produced on a bronchus corresponding to a healthy or slightly altered area, the result is typical atelectasis. If the compression occurs in a bronchus of a previously affected zone, an infiltration takes place, with little reduction in volume. In both situations bronchiectasis results. The longer the obstruction is present and the more intense the infiltrative lesions, the more frequent is the occurrence of bronchiectasis, a condition due to deficient drainage

Bronchial aspiration, direct cauterization of granular ulcerative lesions and dilation of the stenosis are helpful in treatment. The authors express their hope that streptomycin will be of value in early treatment to prevent adenitis or to induce its rapid regression.

KEITH, Rochester, Minn.

TUBERCULOUS MENINGITIS TREATED WITH STREPTOMYCIN. Z. ERDOS, Paediat. danub. **3**:1 (Jan.) 1948.

The first case was that of a 2½ year old girl in whom tuberculous meningitis developed during her stay in the hospital. Streptomycin treatment was introduced at once; 400 mg. was given intramuscularly every day for three months and 100 mg. intraspinally every other day for two months. Recovery was uneventful and complete. Her general state (temperature, appetite, behavior) improved and the sugar content of the cerebrospinal fluid rose to normal within a few days. The bacilli were, however, recovered by Silverstolpe's method for two months, and it was only then that the protein content and the cell count became normal. No toxic reactions of importance could be observed except a decrease in the caloric reaction.

The second child, a girl 4 years old, was admitted to the hospital in the third week of her illness. Eight hundred milligrams of streptomycin intramuscularly and 250 mg. intraspinally were administered every day. In spite of the double doses, treatment with streptomycin proved to be much less efficient in this child than in

the first one. Some toxic symptoms, such as a decrease in the caloric reaction and anaphylactic phenomena, occurred also in this child but treatment was not discontinued because of them. Streptomycin treatment is indicated in every case of tuberculous meningitis, even if one has to risk such grave side effects as lasting deafness.

FROM THE AUTHOR'S SUMMARY.

THE REAL NATURE OF ALLGERY AND THE SPECIFIC TREATMENT OF TUBERCULOSIS. C. PREISICH, Paediat. danub. **3**:13 (Jan.) 1948.

Allergy is not the result of the interaction of antigen and antibodies. If, however, tuberculin as an allergen is first introduced into an organism, certain proteins are sensitized. If then more tuberculin is introduced, it will react with these specially isosensitized proteins and a new poison, apotuberculin, will result. This acts as a half-antigen, giving rise to allergy and to the production of antibodies. It is only after this process that the action of antibodies begins. They paralyze the half-antigen and lower the allergic level.

If this natural process is imitated by constant administration of small doses of tuberculin to the tuberculous patient, it is possible to support the infected organism in its fight against the disease. Intranasal drips are the best means for continuous tuberculin supply. Several patients treated in this manner proved the excellent effect and the innocuousness of the daily intranasal administration of cautiously increasing doses of tuberculin.

FROM THE AUTHOR'S SUMMARY.

Diseases of Blood, Heart and Blood Vessels and Spleen

CONGENITAL AORTIC ATRESIA. L. A. SOLOFF, Am. Heart J. **37**:123 (Jan.) 1949.

The author reports a case of congenital aortic atresia in which the necropsy revealed massive enlargement of the right auricle and right ventricle, a small left auricle and a rudimentary left ventricle. The electrocardiogram showed left axis deviation. The author stresses the electrocardiographic findings, inasmuch as the cardiac lesions would lead one to expect axis deviation to the right.

GIBSON, Chicago.

COMPLETE TRANSPOSITION OF THE AORTA AND A LEVOPOSITION OF THE PULMONARY ARTERY. HELEN B. TAUSSIG and R. J. BING, Am. Heart J. **37**:551 (April) 1949.

A new clinical syndrome is described. The malformation consists of a transposed aorta, a large pulmonary artery which arises primarily from the right ventricle and partially overrides the ventricular septum, a high ventricular septal defect and right ventricular hypertrophy. Clinically, in this instance the heart was but slightly, if at all, enlarged; there were a systolic murmur and thrill. Cyanosis dated from birth. Clubbing of the extremities developed at an early age. The red blood cell count, the level of the available hemoglobin and the hematocrit reading were increased. The electrocardiogram showed evidence of right ventricular hypertrophy. The roentgenograms of the heart showed fulness of the pulmonary conus and increased hilar shadows. On fluoroscopy, the pulmonary vessels showed faint expansile pulsations. The oxygen saturation of the arterial blood was abnormally low and fell still further with exercise. In brief, the clinical syndrome associated with this malformation resembled that of an Eisenmenger complex, except that cyanosis dated from birth.

The two conditions showed a further difference in that in the Eisenmenger complex exercise causes an increase in the consumption of oxygen per liter of ventilation, whereas in this malformation exercise causes a decline in the oxygen consumption per liter of ventilation.

Intracardiac catheterization studies revealed a higher oxygen content in the pulmonary artery than in the femoral artery. It is probable that the volume of blood which entered the pulmonary artery from the right ventricle was equal to that directed from the left ventricle into the aorta. The extensive intimal changes in pulmonary arterioles appeared to be sufficient to account for the increased resistance in the pulmonary vascular bed.

FROM THE AUTHORS' SUMMARY.

CONGENITAL ANEURYSM OF THE RIGHT ANTERIOR SINUS OF VALSALVA (INTERVENTRICULAR ANEURYSM) WITH SPONTANEOUS RUPTURE INTO THE LEFT VENTRICLE. R. O. WARTHEN, Am. Heart J. **37**:975 (May) 1949.

The author reports the case of a 38 year old man who entered the hospital with signs of cardiac failure and cardiac findings suggestive of aortic insufficiency. The autopsy revealed an aneurysm of the right anterior sinus of Valsalva with rupture into the left ventricle. Although an aneurysm of one of the sinuses of Valsalva may theoretically perforate any one of the cardiac chambers, the author was unable to find a previously published report of rupture into the left ventricle.

GIBSON, Chicago.

FUNCTIONAL SYSTOLIC MURMURS IN CHILDREN. CHARLES R. MESSELOFF, Am. J. M. Sc. **217**:71 (Jan.) 1949.

The various features of functional murmurs heard in 300 school children are analyzed. These features include the site of maximum intensity, quality, intensity, duration and effects of change of position and of exercise on the audibility of the murmurs.

It is emphasized that apparently no pathognomonic feature distinguishes a functional from an organic murmur. The only valid means of differentiating the two is to examine each child thoroughly and carefully. This procedure has been shown to lead to correct evaluation of the systolic murmurs in the majority of patients. The lack of pathologic significance of functional murmurs in otherwise normal children and the harm of restricting physical activities for such children are discussed.

HENSKE, Omaha.

THE DIRECTION OF THE PRECORDIAL T WAVE IN THREE HUNDRED AND TWENTY-ONE NORMAL INFANTS AND CHILDREN. LAWRENCE KUSKIN and LOUIS BROCKMAN, Am. J. M. Sc. **218**:65 (July) 1949.

The direction of the T wave in five precordial leads was studied on 321 normal infants and children. The T wave in CF_1 was inverted in 100 per cent of 129 children from 0 through 6 years of age inclusive, except for one diphasic wave in a 5 year old child. No upright T was noted for these children. The T wave in CF_2 was inverted in 90 per cent of the children up to 4 years of age. The T wave in CF_3 followed the same general pattern as in CF_2. The T wave in CF_4 was inverted in the tracings of only 27 of the 321 children (8.3 per cent), and in 20 it was diphasic. There was no inversion in those of 50 children, aged 12 through 14 years. The T wave in CF_5 was inverted in 6 per cent of the

records for children up to 2 years of age, with no inversions thereafter. It is suggested that leads CF_1 and CF_2 offer no significant information that is not contained in leads CF_3, CF_4 and CF_5.

HENSKE, Omaha.

THE SURGERY OF PATENT DUCTUS ARTERIOSUS. JOHN C. JONES, Ann. Surg. **130**:174 (Aug.) 1949.

Before advising surgical treatment of a patient with an uncomplicated patent ductus arteriosus, one must consider the chances of the development of complications in the untreated condition and the dangers of surgical intervention. The author advises operation on all patients with this lesion except those older than 25 years of age, and those who have no progressive cardiac hypertrophy or incapacitation by virtue of having had a fistulous shunt for so long. The optimum age for operation is 3 or 4 years. The patient with patent ductus arteriosus complicated by subacute bacterial endarteritis should be operated on only after prolonged and intensive penicillin therapy. A brief review of the development of the operative technic is presented. The postoperative complications and the end results of 125 operations for patent ductus arteriosus are reported.

BARTIN, Omaha.

STUDIES OF CONGENITAL HEART DISEASE: I. TECHNIQUE OF VENOUS CATHETERIZATION AS A DIAGNOSTIC PROCEDURE. L. DEXTER, F. W. HAYNES, C. S. BURWELL, E. C. EPPINGER, R. E. SEIBEL and J. M. EVANS, J. Clin. Investigation **26**:547 (May) 1947.

Venous catheterization using the technic of Cournand and Ranges was described. Certain modifications were used. The patient was placed on a soft radiolucent mat to give comfort and to avoid venous spasm. Penicillin was given before and after the procedure. Measurement of oxygen consumption, venous catheterization with multiple sampling from the cardiac chambers and arterial puncture were done in sequence, rather than simultaneously. Blood samples and pressures were obtained first from the pulmonary artery, next from the right ventricle and finally, from the right auricle and the superior vena cava. Clotting in the catheter was avoided by an injection of heparin before each sample was withdrawn.

Cardiac output was determined by use of the Fick formula. Formulas were derived for measurement of flow through right to left or through left to right shunts.

Complications of the procedure observed were venospasm with apprehension and discomfort, ventricular extrasystoles and transient auricular fibrillation (of a half-hour's duration). No evidence of pulmonary embolism from clot formation around the catheter was seen. Ten patients subjected to this technic died at a later date, and postmortem examinations were performed. In no case was death attributable to the catheterization, and there were no demonstrable lesions of veins, heart, pulmonary artery or lungs attributable to passage of catheter.

BRODSKY, Cincinnati.

STUDIES OF CONGENITAL HEART DISEASE: II. THE PRESSURE AND OXYGEN CONTENT OF BLOOD IN THE RIGHT AURICLE, RIGHT VENTRICLE, AND PULMONARY ARTERY IN CONTROL PATIENTS WITH OBSERVATIONS ON THE OXYGEN SATURATION AND SOURCE OF PULMONARY "CAPILLARY" BLOOD. F. W. HAYNES, C. S. BURWELL, E. C. EPPINGER, R. D. SAGERSON and J. M. EVANS, J. Clin. Investigation **26**:554 (May) 1947.

Oxygen contents of blood and pressures in various parts of the pulmonary artery, right auricle and right ventricle were studied in control patients with various diseases but without any evidence of congenital heart disease.

Systolic and diastolic pressures were recorded through the catheter with a Hamilton manometer. Pressures in the pulmonary artery and right ventricle were identical within the limit of respiratory variations in each of the patients examined. The values for blood pressures in the pulmonary artery and right ventricle were 20 to 30 mm. of mercury systolic and 8 to 12 mm. diastolic, while the right auricular pressure was 8 to 20 mm. of mercury systolic and 0 diastolic.

Oxygen contents of the superior vena cava were as much as 19 volumes per cent lower than those of the right auricle. The greatest increase in oxygen content observed in going from the right auricle to the right ventricle was 0.9 volume per cent, and from the right ventricle to pulmonary artery, 0.5 volume per cent. The oxygen content of bloods obtained from various sites within the right auricle and right ventricle showed considerable variation at times, while those from the pulmonary artery were quite constant. The authors concluded that mixed venous blood for the determination of cardiac output may be obtained consistently from the pulmonary artery.

BRODSKY, Cincinnati.

STUDIES OF CONGENITAL HEART DISEASE: III. VENOUS CATHETERIZATION AS A DIAGNOSTIC AID IN PATENT DUCTUS ARTERIOSUS, TETRALOGY OF FALLOT, VENTRICULAR SEPTAL DEFECT, AND AURICULAR SEPTAL DEFECT. L. DEXTER, F. W. HAYNES, C. S. BURWELL, E. C. EPPINGER, M. C. SOSMAN and J. M. EVANS, J. Clin. Investigation **26**:561 (May) 1947.

Six cases of congenital heart disease were studied with the technic of venous catheterization. One case of patent ductus arteriosus, 2 of tetralogy of Fallot, 1 of interventricular septal defect and 2 of interauricular septal defect comprised the group studied.

In the case of patent ductus arteriosus, the oxygen content of the blood in the pulmonary artery was higher than that of the right ventricle. After ligation of the ductus, the oxygen contents of the bloods from these sites were equal.

In the case of tetralogy of Fallot, the pulmonary stenosis was identified by the finding of a higher systolic pressure in the right ventricle than in the pulmonary artery. In another case, the catheter passed into the right ventricle, through the septal defect and into the aorta. The pressures in the aorta and right ventricle were equal. The oxygen content of the aorta was higher than that of the right ventricle. Because of these observations, plus those obtained on the clinical examination, in which a machinery-like murmur was heard over the precordium, a diagnosis of the tetralogy of Fallot with patent ductus arteriosus was made. In the case of interventricular septal defect, the blood in the right ventricle was more highly oxygenated than that in the right auricle.

In the 2 cases of interauricular septal defect studied, 1 was recognized by introducing the catheter through the defect and obtaining highly oxygenated blood from the left auricle, while the other was diagnosed by finding arterial blood in the right auricle.

The cardiac output and the blood flow through the shunts were calculated with the use of the Fick principle in all cases. Roentgenograms of the catheter tip in various sites of the cardiac chambers were shown.

BRODSKY, Cincinnati.

STUDIES OF BLOOD VOLUME IN THE TETRALOGY OF FALLOT AND IN OTHER TYPES OF CONGENITAL HEART DISEASE. WOODROW NELSON, H. S. MAYERSON, J. H. CLARK and CHAMP LYONS, J. Clin. Investigation **26**:860 (Sept.) 1947.

Measurements of plasma, red cell and total blood volumes, total circulating hemoglobin and plasma protein were made in 7 cases of tetralogy of Fallot, 4 cases

of isolated septal defect and 1 case each of the Eisenmenger complex, isolated pulmonary stenosis, coarctation of the aorta, congenital mitral stenosis and patent ductus arteriosus.

The data presented showed decided increases in red cell and total blood volumes in all cases of tetralogy of Fallot and in 1 case of pulmonary stenosis. Values as high as 490 and 602 per cent of average normal standards were obtained in 2 cases of tetralogy of Fallot. The plasma volume was at or slightly above standard levels. No significant correlation was discovered between total blood volume, red cell volume, total circulating hemoglobin or total circulating plasma protein and hemoglobin percentage and hematocrit reading. Plasma protein and total circulating plasma protein were within the standard range. Prolonged rest in bed and production of a new shunt by the Blalock procedure in 2 cases resulted in a gradual decrease of red cell volume toward standard values. The cases of congenital mitral stenosis and patent ductus arteriosus showed high total blood, red cell and plasma volumes. Cases of intraventricular septal defect, Eisenmenger complex and coarctation of aorta showed blood volumes at standard levels.

The authors suggest that blood volume determinations be used as a supplementary study in the differential diagnosis of various types of heart disease and for indication of the optimal time for surgical intervention in these cases.

BROOSKY, Cincinnati.

CHANGES IN THE BONE MARROW IN MEGALOBLASTIC ANEMIAS OF INFANCY BEFORE AND AFTER FOLIC ACID THERAPY. W. W. ZUELZER, A. NEWHALL and L. HUTOFF, J. Lab. & Clin. Med. **32**:1217 (Oct.) 1947.

In 1946, the senior author described an anemia of infancy characterized by macrocytosis, hyperchromia, achlorhydria and a specific response to folic acid. In this paper serial studies of the tibial bone marrow during folic acid therapy (10 to 100 mg. daily) are presented. Prior to therapy the predominating cell in the erythroid series was megaloblastic or intermediate in development between this stage and the normoblastic. Within twenty-four hours after the institution of folic acid therapy a clearcut change in the direction of normoblastic marrow was noted; in fact, the actual volume of the erythroid elements in the marrow increased. The data amplified those previously obtained by the authors with regard to the response of these patients to folic acid.

FORBES, St. Louis.

BACTERIAL ENDOCARDITIS (STREPTOCOCCUS VIRIDANS) IN AN EIGHTEEN-MONTHS OLD INFANT SUCCESSFULLY TREATED WITH PENICILLIN. M. J. HERON and S. G. ROSS, Canad. M. A. J. **59**:367 (Oct.) 1948.

A rare case of endocarditis in an 18 month old infant due to a Streptococcus of the viridans group is reported. Treatment consisted of massive doses of penicillin, totaling 26,000,000 units over a period of thirty-nine days. There was no sign of relapse six months later.

MCGUIGAN, Evanston, Ill.

UNTOWARD EFFECTS OF INJECTIONS OF BLOOD IN INFANCY. E. STRANSKY and D. DAUIS-LAWAS, Ann. pædiat. **170**:21 (Jan.) 1948.

After an injection of blood at the age of 2 months, malaria and infectious hepatitis developed in a 3 week old infant. The symptomatology and management of both diseases are shortly discussed. The literature and the means of prophylaxis are reviewed.

FROM THE AUTHORS' SUMMARY.

DIAGNOSIS AND TREATMENT OF A PATIENT HAVING "SPORADIC" HEMOPHILIA WITH MULTIPLE HEMARTHROSES. PIERRE GIRARDET, Ann. pædiat. **170**:169 (April) 1948.

A boy 11 years of age had cutaneous, subcutaneous, renal and articular hemorrhages and a prolonged clotting time. The clinical and roentgenologic changes in the joints in hemophilia are described. Clinical improvement with shortening of the clotting time took place after oral administration of dried plasma from America. Lengthening of the clotting time was noted when old plasma was used or when the doses were too large. The conditions of clotting were investigated in another patient who was suspected to have hemophilia because his plasma failed to have any effect on the plasma of a known hemophiliac patient. Further tests showed that dried plasma may have a retarding or an accelerating action on clotting according to the concentration and the age of the solution. This action was observed in healthy and hemophiliac persons alike. In the latter it first accelerated and then prolonged clotting considerably, whether administered by mouth or intravenously. Some hypothetic explanations are offered.

FROM THE AUTHOR'S SUMMARY.

HEREDITARY AND SYMPTOMATIC CONGENITAL THROMBOPENIA. FRITZ HAUSER, Ann. pædiat. **171**:86 (Aug.) 1948.

A case is described in detail of essential thrombopenia in an infant whose mother also had thrombopenic purpura (Werlhof's disease). Three cases of transitory thrombopenia with hypoprothrombinemia are briefly mentioned. The cases in the literature are discussed, those of congenital thrombopenia in children whose mothers had the same disease being separated from thrombopenias of other origins. This series and a number of cases in the literature demonstrate that essential thrombopenia, or Werlhof's disease in the stricter sense, may be hereditary.

In analogy to the usual separation of essential from symptomatic thrombopenia, it is proposed to divide the cases in infancy into hereditary and symptomatic types. Symptomatic thrombopenia in the newborn is probably caused by a transitory deficiency in thrombocytes in an otherwise healthy mother during pregnancy, or by a deficiency in thrombocytes in an infant with a coexisting disturbance in coagulation of different causation, as lack of prothrombin. There remains another group of cases with absence of giant cells in the bone marrow (congenital hypoplastic thrombopenia). The authors who described these cases were of the opinion that a malformation of the megakaryocyte mechanism existed, which again would point to hereditary factors.

FROM THE AUTHOR'S SUMMARY.

HOOKWORM ANEMIA IN CHILDREN. EUGENE STRANSKY and DOMICIANA F. DUIS-LAWAS, Ann. pædiat. **171**:121 (Sept.) 1948.

Fourteen cases of hookworm anemia in children are discussed; 1 case of an adult is added. Blood and bone marrow examinations and findings, blood serum chemistry (hypoproteinemia), examinations of feces, diagnosis and treatment are discussed. Although hookworm anemia is microcytic in the majority of the cases, macrocytosis is not exceptional, while hypochromia is a constant feature of the condition.

Fourteen of the 15 cases were of anemia of the regenerative type, while a single case was of aplastic anemia (panmyelophthisis). Thirteen of the 15 cases were of males and only 2 of females.

The cause of hookworm anemia is considered to be as follows: (*a*) the blood-sucking parasite causes loss of blood; (*b*) the demand for iron and protein is

increased in order to maintain an approximately normal hemoglobin concentration and serum protein level; (*c*) if the increased demand can be satisfied, there will be no development of anemia; if not, the developing anemia may be severe; (*d*) besides iron and protein deficiency, multiple vitamin deficiency and secondary infections may be additional factors.

Several case reports prove that when sufficient amounts of iron and protein are administered the improvement is rapid. Secondary infections greatly delay the improvement.

A case of hookworm anemia of the mother and subsequent severe iron deficiency anemia of the infant early in life is reported, while a second case is briefly mentioned. The anemia of the infant was due to lack of sufficient iron storage during fetal life on account of the iron deficiency of the mother.

FROM THE AUTHORS' SUMMARY.

ON IRON DEFICIENCY ANEMIA IN INFANCY AND CHILDHOOD IN THE TROPICS. EUGENE STRANSKY and DOMICIANA F. DAUIS-LAWAS, Ann. pædiat. **171**:139 (Sept.) 1948.

Iron deficiency anemia is extremely widespread in children in the first year of life in the Philippines, due either to prolonged, exclusive breast feeding or to prolonged, exclusive artificial feeding with milk formulas. Even when additional food is administered, it is too poor in iron to satisfy the daily requirement of 6 mg. Of the children examined 80 per cent showed a hemoglobin level below 10 Gm. and 56 per cent below 9 Gm. per hundred cubic centimeters. In those in the age groups from 6 months to 2 years, all observed cases of anemia were due to iron deficiency; in those from 2 to 5 years of age, 90 per cent of anemias were of the iron deficiency type, although many children had hookworm anemia; 60 per cent of the anemias in children of this age were due to hookworm infection.

As the anemia of pregnancy (iron deficiency anemia of pregnancy) is widespread in the Philippines, so much so that scarcely a woman in the poorer classes of the population has a normal hemoglobin level, it is probable that the iron storage of the fetus is insufficient and that the infant is born with iron deficiency. This may be a further reason for the development of iron deficiency anemia.

Iron deficiency anemia can be prevented and cured by the use of any food rich in iron, provided there is no secondary infection. Our treatment has been either addition of hemo® to the food or administration of bivalent inorganic iron salts.

Iron deficiency anemia leads to decreased resistance, hence the possibility of secondary infections. Such infection causes further decrease in the hemoglobin level and red blood cell count. Through aggravation of the anemia, the infection may be fatal. By prevention of iron deficiency anemia, the morbidity and mortality among children not only in the first year but in the first five years of life could be considerably decreased. We suggest for the prevention of iron deficiency anemia both the administration of food rich in iron in infancy and the use of table salt enriched with ferrosulfate for pregnant women and older children.

The causation, symptomatology, distribution in persons of different ages, therapy and prevention of iron deficiency anemia are discussed.

FROM THE AUTHORS' SUMMARY.

CARDIAC HYPERTROPHY IN UNDERNOURISHED CHILDREN. T. WEGMANN, Schweiz. med. Wchnschr. **78**:295 (April 3) 1948.

The author examined 1,000 French children who were war casualties and supposedly pretuberculous. On roentgenologic examination the heart shadow was increased in all directions and in many instances the right side of the heart was enlarged and the more affected. Some of these children showed tachycardia, and fluctuations in and loss of weight; many showed great protrusion of the abdomen and lordosis. On auscultation soft systolic murmurs, especially near the apex, were frequently noted. Percussion showed an increase in the breadth of the heart. The author, after considering the causation, advanced the opinion that a hypovitaminosis or a deficiency in vitamin B_1 might be the underlying cause. The author undertook the estimation of vitamin B in the urine of 20 of these children and found it diminished. In those children with a definite increase in the size of the heart, there was little or no vitamin B in the urine examined. The transverse diameter of the heart diminished in size when the children were given a suitable diet, including legumes, eggs and meats and a vitamin B_1 preparation. He is reminded of the heart changes in patients with beriberi and states the view that these war children had a similar vitamin B deficiency. ABT and ABT, Chicago.

AFIBRINOGENEMIA. I. BIDDAU and L. AMMANITI, Arch. ital. e pediat. e puericolt. **11**:374, 1946.

The authors report the case of a 6 year old girl, of normal constitution, who from birth had frequent bleeding, usually cutaneous, after slight traumas or wounds. There was a history of familial consanguinity, but no evidence of familial hemorrhagic diathesis.

Repeated studies showed a complete lack of blood coagulability with a decreased amount, and occasional absence, of fibrinogen in the blood.

At 9 years of age, after her discharge from the hospital, she died with an acute abdominal syndrome.

The authors discuss differential diagnosis among the various hemorrhagic syndromes and, on the bases of their own clinical and laboratory studies, describe this case as an instance of congenital constitutional afibrinogenemia.

The authors review the few cases reported in the literature, describe the clinical, biochemical and pathologic picture of the disease and discuss its pathogenesis and treatment.

FROM THE AUTHORS' SUMMARY.

PERNICIOUS ANEMIA IN A BREAST-FED INFANT. RICCARDO SCAPATICCI, Arch. ital. pediat. e puericolt. **11**:350, 1946.

A case of pernicious anemia in a child 11 months of age who was exclusively breast fed is described.

The author, after describing the blood, bone marrow, histologic and postmortem pictures, stresses the lack of reaction to blood transfusions and intensive liver therapy.

He is of the opinion that in the pathogenesis of the disease, great importance should be attached not only to the deficiency of the Castle factors (as shown by a negative reaction to the reticulocyte test [Singer] in the rat) but also to the failure of peripheral utilization of the anti-pernicious-anemia principle.

FROM THE AUTHOR'S SUMMARY.

ELECTROCARDIOGRAM OF THE NORMAL INFANT. G. GASPARI, Clin. pediat. **30**:333 (May) 1948.

The characteristics of and physiologic variations in the electrocardiogram of the healthy infant are listed.

HIGGINS, Boston.

PLASMA PROTEIN LEVEL, HEMATOCRIT READING AND OXYGEN CONTENT IN THE BLOOD OF INFANTS WITH ACUTE DIGESTIVE DISTURBANCES. G. C. ALBA, Lattante **18**:21 (Jan.) 1947.

The author followed the clinical course of 11 infants with toxic diarrhea and 3 with "atrophy" through frequent hematocrit determinations and blood chemical analyses.

HIGGINS, Boston.

A CONGENITAL CARDIAC DEFECT IN A NEWBORN INFANT: ANATOMICOPATHOLOGIC REPORT OF A CASE. G. BIANCHI, Lattante **18**:26 (Jan.) 1947.

A fetal heart murmur suggested a congenital cardiac malformation before a child was born. The child died shortly after birth. Autopsy revealed chronic endocarditis with stenosis of the tricuspid valve.

HIGGINS, Boston.

A CLINICAL AND ANATOMICOPATHOLOGIC CONTRIBUTION TO THE STUDY OF LEDERER'S ANEMIA. A. CROSCA, Lattante **19**:81 (Feb.) 1948.

A baby boy 6 months of age became acutely ill with fever and diarrhea, followed by dyspnea, restlessness, pallor and jaundice. After a transfusion, the infant had a striking rise in temperature, with convulsions, and died. A necropsy was performed. Lederer's anemia is an acute hemolytic anemia, the course and symptoms of which are similar to those of favism. While the clinical course is characteristic, the origin is obscure; an allergic phenomenon of a toxic-infectious nature is suggested as the cause.

HIGGINS, Boston.

EOSINOPHILIA IN BONE MARROW AND BLOOD IN THROMBOPENIA. G. TONIOLO and LAURA ANTI, Lattante **19**:232 (April) 1948.

Three cases of thrombopenic purpura are reported in children 4, 4½ and 7 years of age. In the first days of the disease, thrombocytes and polymorphonuclear eosinophils were practically absent from the blood smears; two to three weeks later, the thrombocytes had returned to normal and the eosinophils had reached about 10 per cent of the total white blood cell count. However, in the bone marrow smears from sternal punctures, at first 12 to 18 per cent of the pregranulocytic cells were eosinophilic; as the patients' conditions improved, the number was reduced by half. The authors agree with the opinion of Dameshek that eosinophilia in the marrow cells in thrombopenia indicates a secondary purpura, probably on an allergic basis.

HIGGINS, Boston.

DAILY CURVE OF THE PULSE RATE IN INFANTS. C. IMPERATO and L. LANDUCCI, Lattante **19**:257 (May) 1948.

The curve for pulse rate for 8 infants under 6 months of age while quiet varied on the average during the day from 120 to 128; the pulse rate was highest between noon and 9 p. m. and lowest between midnight and 6 a. m. Similar observations on 6 infants between 6 and 12 months of age showed a wider deviation in the pulse

rate at different times of the day; the rates varied between 104 and 122 beats per minute, the highest peak of the curve being at noon and the lowest depression at 3 a. m.

HIGGINS, Boston.

CLINICALLY AND MORPHOLOGICALLY ATYPICAL CASES OF ACUTE LYMPHATIC LEUKEMIA IN INFANTS. EDMONDO CIFARELLI, Pediatria **56**:37 (Jan-March) 1948.

While describing 3 cases of acute lymphatic leukemia in children, which began and progressed with neoplastic symptoms, the author points out the morphologic characteristics resulting from the patients' great immaturity and his observation of atypical forms of the cells in the myelograms and hemograms.

FROM THE AUTHOR'S SUMMARY.

SICKLE CELL ANEMIA IN A BABY TWENTY-SIX MONTHS OLD, WITH SPECIAL EMPHASIS ON THE PATHOGENESIS OF ACUTE PHASES OF THE DISEASE. ARMANDO CARNEVALE, Pediatria **56**:138 (Jan.-March) 1948.

A case of sickle cell anemia in a 26 month old white child is described. During the hemolytic crisis, a diminution of the sickle cells and a conspicuous increase in the reticulocytes were observed. (The reticulocytes proved to be, in vitro, more resistant toward the sickling process.)

The pathogenesis of the hemolytic crisis seems to depend on the accumulation in the circulatory system of the rigid, inflexible and long sickle cells; these precipitate into the capillaries, causing obstructions and the formation of thrombi. The thrombi, aided by the increased rate of coagulation of the blood in this phase, tend to expand to the size of the vessels of larger caliber. The resolution of the thrombi, caused by the destruction of their constituent elements by the reticuloendothelial cells, leads to the onset of the hemolytic phase, in which most sickle cells are destroyed and replaced by young red cells; these cells are more resistant to the sickling phenomenon and more suitable for vital processes.

FROM THE AUTHOR'S SUMMARY.

PERNICIOUS ANEMIA IN A BOY FOURTEEN YEARS OLD. AKSEL K. F. JACOBSEN, Nord. med. (Hospitalstid.) **33**:1469 (July 4) 1947.

A boy had had asthma until he was 10 years of age, but otherwise he was healthy before the onset of the anemia. This manifested itself three months before his admission to the hospital with increasing fatigue and later with diarrhea of nonspecific origin and stools of gruel-like consistency. The diarrhea had stopped one week before his admission. The diet had been adequate before the illness started. When first seen, his temperature was 38.4 C. (101 F.); his skin was of a greenish yellow pallor, and he was greatly emaciated. The hemoglobin concentration was 30 per cent; red blood cells numbered 1,050,000. The color index was 1.5; white blood cells were 1,360, with 20 to 30 per cent small and large lymphocytes and a shift to the right of the leukocytes without any abnormal cells. On two occasions 2 and 3 per cent myelocytes were seen. The red blood cells showed poikilocytosis and anisocytosis, with a preponderance of megalocytes, cells with basophilic granules and normoblasts. Sternal puncture revealed 15 per cent erythroblasts, 24 per cent megaloblasts, 23 per cent normoblasts, 25 per cent lymphocytes, 3.5 per cent hemocytoblasts, 10 per cent myelocytes, 3.5 per cent metamyelocytes, 16.5 per cent rod-shaped nucleated leukocytes and 2 per cent leukocytes with segmented nuclei. The sedimentation rate was 26 mm. There

were 120,000 thrombocytes. The clotting and bleeding times were normal. Achlorhydria was detected and there was no free acid after the histamine test. Roentgenographic examination of the stomach and intestine showed no defect. The stools were essentially normal. Blood transfusions and ferrous compounds were given without effect. The response with liver extract was satisfactory. The boy was discharged from the hospital in good condition with a normal blood picture. In the discussion the author maintains that this was a case of genuine pernicious anemia. The observation time was only three months.

WALLGREN, Stockholm, Sweden.

PAROXYSMAL TACHYCARDIA. R. THELIN, Nord. med. **35**:1556 (July 18) 1947.

A case of paroxysmal tachycardia is reported in a boy 3½ years old who had had two attacks at the time of the report. The heart rate was about 300. The electrocardiogram made during an attack showed a depressed S-T segment and no evident P waves; it was otherwise normal. After the attack the tracing showed no defect. There were enlargement of the heart during the attack and a slight murmur at the apex. The duration of the attacks was two to three days. Treatment with digitalis compounds was without effect. The origin of the disorder was unknown.

WALLGREN, Stockholm, Sweden.

MYOCARDITIS IN INFANTS. WILHELM BERGMAN, Nord. med. (Hygiea) **36**:2111 (Oct. 17) 1947.

Two cases are reported. The first was of a male infant 2½ years of age who previously had had a mild hypertrophic pyloric stenosis. He became acutely ill, with vomiting, malaise and tachycardia. Enlargement of the heart with no murmur was noted. The electrocardiographic tracing was of the coronary type. The heart rate was 115 to 210. He died two months later. Myocardial scars and slight chronic myocardial changes were found, but the coronary arteries were normal. The lungs, liver and spleen were congested. The other case was of a male infant 1½ years old, who suddenly fell ill with catarrhal pulmonary signs and symptoms and was brought to the hospital in an almost moribund condition the same day. He was treated for bronchiolitis and eventually was cured. One week after the manifestation of the illness a long systolic murmur was heard over the heart, but no enlargement was noted at roentgenologic examination and the electrocardiogram after another week showed normal conditions. At his discharge from the hospital no murmur was heard.

WALLGREN, Stockholm, Sweden.

PERNICIOUS ANEMIA IN A CHILD. UNO MURRAY, Svenska läk-tidning. **44**:411 (Feb. 14) 1947.

A Finnish girl, aged 7 years, a single child of an unmarried woman, had displayed periods of fatigue and pallor every spring and fall and had during the last two years been hospitalized four times for severe anemia and albuminuria. When first seen she was thin and pale. The hemoglobin concentration was 78 per cent. Red blood cells numbered 3,930,000 and white blood cells 8,400, with a normal blood picture. Thrombocytes were 211,000. The sedimentation rate was 17 mm. No intestinal parasites were detected. The spleen and the superficial lymph nodes were normal. Albuminuria was noted, with 10 to 15 leukocytes in the urine. The girl was discharged from the hospital in satisfactory condition with residual albuminuria. Two months later a relapse of the anemia occurred. The hemoglobin concentration was 42 per cent. Red blood cells were 2,500,000,

with 12 reticulocytes per thousand cells and 1 per cent nucleated red cells. There were 1,700 white blood cells, with 74 per cent lymphocytes, poikilocytosis and anisocytosis. Thrombocytes numbered 60,000. Sternal puncture showed numerous megaloblasts. The osmotic resistance was normal. The Wassermann reaction was negative. Serum albumin measured 4.4 to 4.6 Gm. and serum globulin 2 to 2.8 Gm. Hydrochloric acid was present in the gastric juice, with a positive reaction to the histamine test. Treatment with a liver preparation was successful, with remission of the pathologic blood picture.

WALLGREN, Stockholm, Sweden.

INTRAOSSEOUS BLOOD TRANSFUSION IN CHILDREN. SVEND HEINILD, Ugesk. f. læger **107**:481 (June 21) 1945.

The author reports his experience with 60 intratibial blood transfusions in 41 children 2 days to 4 years of age. Generally, the amount of blood injected was 20 cc. per kilogram of body weight. Except for a transient hematoma no complications were demonstrable. The bone marrow was normal in the children who were examined post mortem. Three children had hyperpyrexia, an effect which may have contributed to the cause of death. Bronchopneumonia may be regarded as a contraindication to transfusion. The therapeutic effect of the transfusion was good in certain severe infections and hemorrhagic diathesis but was doubtful in dyspepsia. The author recommends caution with bone marrow transfusions in small children.

WALLGREN, Stockholm, Sweden.

A "BLUE BABY" WITH CONGENITAL PULMONARY STENOSIS. I. BOEREMA, Neder. tijdschr. v. geneesk. **92**:184 (Jan. 17) 1948.

For the first time in the Netherlands, the Blalock-Taussig operation was performed on a girl presenting symptoms of the tetralogy of Fallot (ventricular septal defect, pulmonary stenosis or atresia, dextraposition of aorta and hypertrophy of right ventricle). For several short periods the patient rested in bed, and during the last two years she had had several hemoptyses. The latter symptom made the diagnosis somewhat doubtful, but as all the typical symptoms of the tetralogy of Fallot were present, an operation was performed. The left subclavian artery was implanted in the left pulmonary artery. The patient was well during and after the operation; cyanosis diminished greatly, the oxygen saturation of the arterial blood increased from 59 per cent, before the operation, to 85 per cent, two weeks after the operation.

VAN CREVELD, Amsterdam, Netherlands.

DIAGNOSIS OF TETRALOGY OF FALLOT. J. I. DE BRUYNE, S. VAN CREVELD and H. A. P. HARTOG, Nederl. tijdschr. v. geneesk. **92**:481 (Feb. 14) 1948.

Two children, about 6 years old, who had symptoms of the cyanotic type of congenital heart disease, proved to be unsuitable for the Blalock-Taussig operation.

The first child was cyanotic since birth; he had clubbed fingers and toes, right axis deviation, neither convexity nor concavity of the pulmonary region and clear pulmonary fields. No systolic murmur could be heard; the cyanosis was not severe and was certainly not sufficient to indicate that an extreme narrowing of the pulmonary artery was present. Besides this, the child was able to walk short distances without becoming exhausted. The clinical picture could be explained better by a diagnosis of truncus arteriosus communis.

The second patient showed the classic signs of tetralogy of Fallot, but in addition a continuous murmur, typical of patent ductus arteriosus, could be heard

above the manubrium sterni. The cyanosis had appeared when the child was 3 years old. On fluoroscopy the pulmonary vessels were easily visible. This child will be operated on only if the patent ductus fails to compensate for the insufficient circulation to the lungs.

VAN CREVELD, Amsterdam, Netherlands.

INFECTION AND ANEMIA. J. J. DE JONG, Nederl. tijdschr. v. geneesk. **92**:641 (Feb. 28) 1948.

A boy, 16 years old, had pneumonia associated with hypochromic anemia. The hemoglobin content was 39 per cent and the red blood cell count 2,390,000 per cubic millimeter. Seven days after his recovery from the pneumonia, the hemoglobin content was 55 per cent and the red blood cell count 3,470,000 per cubic centimeter. After ten days' treatment with 400 mg. of a preparation of ferrous chloride and glucose (ferrostabil) the hemoglobin concentration increased to 70 per cent.

There are two theories concerning the cause of anemia in the presence of infections. One group of investigators is of the opinion that the iron of the food and some of the iron in the blood serum are directed to the reticuloendothelial system, where it plays a part in the immunity mechanisms. At the same time iron is of importance in infections as one of the constituents of the leukocytes and as a catalyst for the increased tissue oxidation. Thus, there remains insufficient iron for the formation of hemoglobin and anemia results. As there has been only a transfer of the iron in the body, the hemoglobin content of the blood increases spontaneously after the infection has been overcome. According to other investigators, the anemia is explained as follows: As a result of the infection, the "depot iron" in the reticuloendothelial system is changed into a form which takes part actively in the immunity mechanisms. Furthermore, the amount of iron in the reticuloendothelial system is increased by the take-up of iron liberated during the augmented hemolysis as a consequence of the infection. The bone marrow makes no use of the latter iron as the marrow is inhibited by the presence of the infection in the body, with the development of a hypoplastic anemia.

VAN CREVELD, Amsterdam, Netherlands.

ELECTROCARDIOGRAPHIC STUDY OF PATENT DUCTUS ARTERIOSUS. W. DEN BOER, Nederl. tijdschr. v. geneesk. **92**:698 (March 6) 1948.

The electrocardiogram of the patient with patent ductus arteriosus is generally normal, as the two ventricles are about equally heavily charged. Left-sided preponderance occurs, but in the case of right-sided preponderance a complication must be present, or the diagnosis is wrong.

In 3 children admitted for surgical treatment of patent ductus arteriosus it appeared from the electrocardiogram that a complicating malformation of the heart was present. Operation was, therefore, not indicated.

VAN CREVELD, Amsterdam, Netherlands.

REFRACTORY ANEMIA. J. VAN LOOKEREN CAMPAGNE, Nederl. tijdschr. v. geneesk. **93**:542 (Feb. 19) 1949.

Usually the causes of an anemia can be easily detected; however, sometimes they are diverse and complex. A case of anemia is described and in the discussion on the possible causes 2 other interesting cases are reported. A girl 30 months of age had a relapsing anemia. This anemia was noted for the first time a few weeks after birth, when an increasing pallor of the skin became manifest. She had been treated with iron, liver and blood transfusions, resulting only in temporary improve-

ment. There were no clinical signs of ill-being. In the hospital the main observations were a slight hyperchromic anemia, urobilinuria, normal hydrochloric acid in the stomach and a low number of reticulocytes: 2 to 3 per thousand cells. The bone marrow was normal. The common causes of anemia are briefly discussed and found inapplicable in this patient. Congenital hypoplastic anemia was also taken into consideration.

At this point the author relates the story of one of his patients who had a typical form of this disease. He concluded that the findings in these 2 patients differed in some important points. Finally, the following three causes were considered: ascariasis, deficient diet and incompatibility of the previously received blood. The patient belonged to an Rh-negative group and had frequently received blood from donors whose Rh type was not determined. The author describes another Rh-negative patient in whom the anemia was caused by repeated transfusions of Rh-positive blood. The findings in these 2 patients were greatly analogous. The patient was treated for her ascariasis, and one transfusion of Rh-negative blood was given. A normal diet rich in vitamins was prescribed, and the patient was still improving seven weeks after the transfusion. VAN CREVELD, Amsterdam, Netherlands.

Diseases of Nose, Throat and Ear

INFANTILE OTITIS UNACCOMPANIED WITH OTORRHEA. L. SURJAN, Orvosok lapja **3**:292 (March 9) 1947.

On basis of the specific resistance of the infant and the correlated local symptoms, Surjan classifies infantile otitis, unaccompanied with otorrhea, into five groups. The causes for the absence of secretion can be sought in the anatomic condition of the ear, in the specific resistance of the infant and in external factors. In such cases the only reliable local factor is the reaction perceived when the diseased ear drum membrane is pierced. In the case of inflammation the feeling is that a soft, jelly-like substance has been pierced. If on paracentesis the membrane is found free of disease, it is safe to refuse to perform the operation suggested, perhaps, by the pediatrician. The importance of latent otitis is greater than that of the manifest disease, because it is more frequent and because serious infiltrations may develop without otorrhea. GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

Diseases of Lungs, Pleura and Mediastinum

PULMONARY AGENESIS AND HYPOPLASIA. C. ELAINE FIELD, Arch. Dis. Childhood **21**:61 (June) 1946.

Fourteen cases are reported in detail with roentgenograms and bronchograms. These cases fall into three categories:

1. Five cases of permanent underdevelopment of one lung.

2. Six cases of displacement of the heart and mediastinum in the first year of life, correcting itself within two to three years. It is suggested that this may be caused by a temporary hypoplasia of the lung.

3. Three cases showing a triangular mediastinal opacity in the roentgenogram. The possibility that this is caused by an isolated portion of pulmonary tissue with no bronchial communication is discussed. KELLY, Milwaukee.

COMPLICATIONS OF LOCALIZED PULMONARY EMPHYSEMA IN CHILDHOOD. S. VAN CREVELD and J. VAN DEN BROECKE, Arch. Dis. Childhood **21**:139 (Sept.) 1946.

Two cases are described which clearly illustrate the complications and clinical and roentgenologic signs and symptoms to which localized bullous and interstitial emphysema may give rise in childhood.

The first patient, an infant, showed a definite pneumopericardium occurring as a complication of bronchopneumonia. Attacks of cyanosis and increased cardiac sounds provided clinical confirmation of the diagnosis.

The second patient, a girl aged 5 years, showed symptoms and signs of bullous and subcutaneous emphysema occurring simultaneously, with, in addition, roentgenologic evidence of mediastinal emphysema and air situated around the heart. Here the localized bullous emphysema must have preceded the occurrence of the interstitial emphysema. Attention is drawn to the particular clinical signs which were present in this child.

KELLY, Milwaukee.

CONGENITAL CYSTIC DISEASE OF THE LUNG. ROBERT M. LEVINE, Canad. M. A. J. **62**:181 (Feb.) 1950.

The literature on congenital cystic disease of the lung is briefly reviewed and one case each of solitary and multiple cysts presented. Both patients were treated successfully by pneumonectomy.

MCGUIGAN, Evanston, Ill.

WASSERMANN-POSITIVE BRONCHOPNEUMONIA IN CHILDREN AND ITS SPECIAL FORMS (FANCIONI-HEGGLIN SYNDROME). CONRAD GASSER, Helvet. paediat acta **2**:185 (June) 1947.

Fifty cases of Wassermann-positive pneumonia observed at the children's hospital at Zurich, Switzerland, are reviewed. The exciting cause was considered in the majority of cases to be a virus. In addition, an endogenous predisposition was necessary for the disease to be manifest with a positive Wassermann reaction. Pairs of children of the same parentage who were simultaneously ill gave different reactions. The allergic manifestations, the catarrhal susceptibility and the degenerative stigmas supported a constitutional factor.

Certain cases could not be explained as due to a virus infection. Owing to the nonspecificity of the antigens, a pseudosyphilitic syndrome can arise from most diversified origins. Quantitatively, the syphilitic reactions differed strongly and the degree of reaction did not run parallel to the severity of the disease. Cerebrospinal fluid findings positive for syphilis were not observed. The reaction to the cold agglutination test was but rarely positive. Bacteriologic investigations were of no avail. Chemically, the blood showed a relative increase of the globulins. The erythrocyte sedimentation reaction was increased. The blood picture usually showed neutrophilic leukocytosis with persistence of eosinophils. Tuberculosis, which clinically runs a similar course, on account of its positive reaction to tests for syphilis, had to be defined by differential diagnosis. A spontaneous negative reaction later contradicted syphilis. Differential diagnosis from other types of virus pneumonia was difficult.

Therapy was generally superfluous. Frequently, sulfanilamide and penicillin resistance was present.

Prognostically, only the miliary forms could be evaluated as of serious significance. No fatal outcome was observed. Unusual forms encountered in the present series were 7 cases of miliary bronchopneumonia, several with severe manifestation; 1 case of bronchopneumonia with a Wassermann-positive reaction,

being the second appearance of the disease; 2 cases of pneumonia occurring after injection of foreign serum, one appearing as the migratory type in conjunction with eosinophilia and interpreted as equivalent to serum sickness; several cases of pneumonia associated with measles with a positive syphilitic reaction, appearing partly as a secondary illness (*zweites Krankstein*) after measles.

From the Author's Summary.

Bronchopulmonary Segments. Eduardo Rivero, Rev. cubana de pediat. **19**:129 (March) 1947.

The author discusses the various methods of describing pulmonary structure. Actually, the bronchopulmonary segments are considered the true physiopathologic units of the respiratory organs. Each segment of practically constant localization receives its aeration from a constant bronchus. An understanding of this is necessary for cooperation among the clinician, the bronchoscopist, the roentgenologist and the surgeon, as well as the pathologist. The classifications of Kramer and Glass, of Chevalier Jackson and of Foster-Carter and Hoyle are discussed. In the author's opinion, the last-named classification is the most satisfactory. The segments as listed by Foster-Carter and Hoyle are described and well illustrated.

Keith, Rochester, Minn.

Bronchography with Iodized Oil: A Harmful Diagnostic Procedure. F. K. Fischer, Schweiz. med. Wchnschr. **80**:273 (March 18) 1950.

In the case of a 50 year old man iodized oil was used for bronchography. Five and a half months later a pneumonectomy was performed when carcinoma was suspected. The patient died. In the lungs foreign body granulomas (due to oil) were found. On roentgen examination definite remnants of iodized oil could be demonstrated. Fischer warns against the use of iodized oil in bronchography. Other iodine compounds, such as joduron B, are preferable.

Amberg, Rochester, Minn.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

The Treatment of Congenital Atresia of the Esophagus with Tracheo-Esophageal Fistula. I. A. Bigger, Ann. Surg. **129**:572 (May) 1949.

Congenital atresia of the esophagus occurs once in approximately 2,500 births, or with about the same frequency as harelip and cleft palate. It may occur either with or without a fistulous communication with the trachea. Complete anatomic diagnosis is necessary for treatment. The author stresses the importance of a careful history, the use of a soft rubber catheter passed into the esophagus to determine the point of atresia and the use of roentgenoscopic and roentgenographic examinations following the injection of iodized oil into the upper part of the esophagus. Barium sulfate should never be used for this purpose.

A plan of management is outlined, including certain details of operative technic under which satisfactory results have been obtained in a small group of infants with congenital atresia of the esophagus and tracheoesophageal fistula.

Bantin, Omaha.

Thyroglossal Cysts and Sinuses. Samuel F. Marchall and Walter F. Becker, Ann. Surg. **129**:642 (May) 1949.

Thyroglossal cysts, sinuses or fistulas constitute one of the commonest congenital anomalies arising in the neck. They occur in the midline of the neck at any

level from the base of the tongue downward to the suprasternal notch. Cysts are found more commonly below the hyoid bone than above it. Successful treatment of this condition is dependent on complete removal of the entire thyroglossal tract, which must include excision of the central part of the hyoid bone and the tract extending above the hyoid to the cecal foramen.

BANTIN, Omaha.

INTUSSUSCEPTION IN INFANTS AND CHILDREN: A REPORT OF 143 CONSECUTIVE CASES. WILLIAMS H. SNYDER JR., ALFRED R. KRAUS and LAWRENCE CHAFFIN, Ann. Surg. **130**:200 (Aug.) 1949.

During the last ten years the over-all mortality rate of intussusception at the Children's Hospital, Los Angeles, has been 4.8 per cent. In 125 consecutive cases, in which operation was performed with reduction or resection, the mortality rate was 4 per cent. From a clinical standpoint, the authors recognize two types of intussusception: Type I, in which the intussusceptum is tightly held by the intussuscipiens, causing interference with blood supply and complete obstruction, and type II, in which the intussusceptum is loosely held and, therefore, at first causes only partial obstruction and little vascular damage.

The importance of preoperative care is emphasized. Intranasal gastric suction is indicated in all cases. Water, salt and dextrose are given in those cases in which there is evidence of loss of these essentials. Blood is given to those patients who are in poor condition (10 cc. per pound [0.5 Kg.] of body weight as the initial amount). Antibiotics and chemotherapeutic agents should be administered to the clinically ill patients. Patients in whom there is a little damage to the intussusceptum require no special postoperative therapy. Patients in whom a resection has been necessary or in whom there has been severe damage to the intussusceptum are given strenuous postoperative care. Constant suction is maintained. Blood plasma and saline and dextrose solutions are administered parenterally. Oxygen tents are used. Penicillin, streptomycin and sulfadiazine are given in full therapeutic dosages.

BANTIN, Omaha.

COMPLETE DUPLICATION OF THE LARGE BOWEL TREATED BY SUBTOTAL COLECTOMY. CHARLES A. ALLARD, DUDLEY E. ROSS and J. F. HOPKIRK, Ann. Surg. **130**:249 (Aug.) 1949.

A case of complete duplication of the colon with urethral fistula is described and well illustrated. Treatment by subtotal colectomy with preservation of the rectum is described.

BANTIN, Omaha.

THE CELIAC SYNDROME. J. A. JOHNSTONE and P. J. HOWARD, J. Pediat. **35**:1 (July) 1949.

The celiac syndrome and hypothyroidism are similar in that both produce abnormalities in the metabolism of protein, fat, carbohydrate and calcium. In addition, Johnstone and Howard are of the opinion that delayed bone age, retardation of growth before abnormal stools appear and the common appearance of celiac symptoms during a decelerating phase of growth are all suggestive signs of thyroid deficiency in this disease. They recognize the importance of infectious, allergic and emotional factors in producing the symptoms of celiac syndrome; they recommend the administration of the usual high protein, high vitamin diet in its management. The thyroid, they say, is sometimes but not always involved. The defect may be thyroid deficiency or it may be secondary hypothyroidism

resulting from nitrogen and caloric deficits. Thyroid therapy shortens the duration of symptoms in some cases of celiac syndrome. When it appears that the hypothyroidism is secondary to nutritional deficits, thyroid is used in small doses for its anabolic effect.

MACDONALD, Pittsburgh.

ESOPHAGEAL ATRESIA WITH TRACHEOESOPHAGEAL FISTULA: EPIDEMIOLOGIC AND TERATOLOGIC IMPLICATIONS. THEODORE H. INGALLS and RICHARD A. PRINDLE, New England J. Med. **240**:987 (June 23) 1949.

The authors review 107 cases of esophageal atresia, 102 of which included a tracheoesophageal fistula. In many cases there were developmental anomalies of other systems. The abnormality is described as probably developing in the fifth or sixth week and a comparison is drawn with mongolism, wherein aberrant departure from the usual developmental sequences occurs at a similar point.

No hereditary pattern was derived from a study of these cases; in no case was there a repetition in the same or successive generation. Antepartum hemorrhage in the first trimester of pregnancy occurred in 6 instances. Infection or metabolic disturbance in the same period occurred in 6 mothers. The authors infer that these phenomena, along with the presence of polyhydramnios and the occurrence of twins, are significantly involved in possible etiologic relationships, although they point out that further investigation and observation are necessary. The causative agents must be either genetic or acquired and operative during prenatal life, because the defect is present at birth.

WHEELOCK, Denver.

PYLORIC STENOSIS AND PYLOROSPASM. C. E. HAMILTON, New Orleans M. J & S. J. **101**:482 (April) 1949.

The differential diagnosis of these two conditions is stressed. The point is made that palpation of the tumor is unnecessary to establish the diagnosis of stenosis and that hesitation until it is felt may be dangerous.

MCGUIGAN, Evanston, Ill.

THE MUCOSAL PATTERN OF THE TERMINAL ILEUM IN CHILDREN. JOSEPHINE WELLS, Radiology **51**:305 (Sept.) 1948.

In routine gastrointestinal studies on children under 13 years of age, in the Babies Hospital, New York, it was noted that the pattern of the terminal portion of the ileum was different from that seen in adults. The terminal ileums of 14 normal children were subsequently examined fluoroscopically after oral administration of barium sulfate. In all the children small, round or oval translucent areas were demonstrated in the terminal portion of the ileum filled with barium sulfate, which gave a cobblestone appearance. This is in contrast to the normal adult terminal ileum, in which the mucosal pattern under pressure appears as slender regular lines produced by the mucosal folds. It is postulated that the cobblestone appearance in children is due to numerous collections of lymphoid cells, producing rounded projections above the surrounding mucosa. These were seen at necropsy in an 11 month old child who died, and the roentgenograms of the barium sulfate–filled necropsy specimen of the terminal part of the ileum bore out similar observations on living children. The approximate age at which the adult pattern is reached has not yet been established.

ANSPACH, Chicago.

FOLIC ACID IN COELIAC DISEASE. JOHN DUNCAN HAY, Arch Dis. Childhood **23**:220 (Dec.) 1948.

Twenty-two infants and children considered to have celiac disease were treated for a period with a diet low in fat and high in protein, liver extract and vitamins. Folic acid was then added to the therapy for a comparable period. The clinical condition of the children during these periods was compared by observations on rate of gain in weight and on the macroscopic character of the feces. No conclusive evidence was obtained of any beneficial effect of the folic acid.

KELLY, Milwaukee.

THE RADIOLOGY OF INTESTINAL OBSTRUCTION IN CHILDREN AND INFANTS. J. H. MIDDLEMISS, Arch. Dis. Childhood **23**:247 (Dec.) 1948.

The appearances of mechanical obstruction of the bowel are stasis, as shown by the presence of fluid levels, distention of bowel by gas and absence of gas shadows, or the demonstration of collapsed bowel distal to the obstruction. The site of the obstruction can be localized just distal to the most distal part of distended bowel. In a pediatric department, or indeed in any hospital, the contributions which roentgenologic investigation has to make as an aid to clinical diagnosis may be listed as follows: It is essentially a time-saving factor, often enabling the establishment of earlier diagnosis and so providing for earlier surgical treatment before acute obstruction develops. It may provide a diagnosis in many cases in which the history and clinical signs and observations have failed to do so; this applies particularly to infants. In many instances it may be the means of establishing a diagnosis when the alternative is the spending of a further valuable twenty-four hour period in clinical observation, which in turn may lead only to a delayed exploratory laparotomy. It is especially helpful in the observation of postoperative distention, particularly after the fifth day, when the clinician is on the lookout for the possible development of mechanical obstruction as a postoperative complication.

KELLY, Milwaukee.

DECREASED MORTALITY RATE OF CANCRUM ORIS BY THE COMBINED USE OF PENICILLIN AND SULFONAMIDE TREATMENT. M. M. FARGHALY, J. Roy. Egyptian M. A. **31**:884 (Nov.) 1948.

A great decrease in the mortality rate of cancrum oris (gangrenous stomatitis) followed the use of chemotherapy. The author is of the opinion that this should replace all other known types of treatment.

MCGUIGAN, Evanston, Ill.

SPONTANEOUS PNEUMOTHORAX IN PANCREATIC FIBROSIS WITH BRONCHIECTASIS. G. FANCONI and MARGRIT METAXAS-SÜHLER, Helvet. pædiat. acta **2**:279 (June) 1947.

Various types of pancreatic fibrosis with bronchiectasis associated with the following conditions are described: (1) fatty cirrhosis of the liver and diabetes mellitus; (2) pulmonary stenosis originating in the fetus; (3) hypoproteinemia, especially hypoglobulinemia and edema, and (4) pulmonary atelectasis and emphysema and spontaneous pneumothorax.

There was frequently hypocholesteremia with a low ester quota, both values being normalized by pancreatic preparations.

The hyperglycemic course of the curve for blood sugar is a practical criterion for differential diagnosis from celiac disease. No Rh incompatibility is involved.

FROM THE AUTHORS' SUMMARY.

Book Reviews

Tas ferina. By Jeronimo Pou Díaz. No price given. Pp. 289, with 33 illustrations. Revista española de pediatría, Independencia 25, Zaragoza, Spain, 1949.

Although written in Spanish, this book should have an appeal to anyone interested in the history of immunization to whooping cough. The author has made an exhaustive study of the steps leading up to the present methods. These methods are well discussed in painstaking detail. There is an excellent bibliography from all sources and mention is made of almost every source in the discussion.

This is as good a résumé of the subject of whooping cough immunization as the reviewer has seen, and it well earns a place in the literature of this subject.

Mobilization of the Human Body: Newer Concepts in Body Mechanics. By Harvey E. Billig Jr. and Evelyn Loewendahl. Foreword by Carl H. Young, Ed.D. Price, $2. Pp. 65, with 23 illustrations. Stanford University Press, Stanford, Calif., 1949.

Daily exercises which are carefully planned to meet the needs of the individual person have been proved to be of value in the maintenance of general health and a sense of well-being. Billig and Loewendahl, while teaching the mechanics of good body posture and exercises necessary to develop muscle tonus and strength, also emphasize the importance of relaxation of tight joint capsules, and of contracted fibrous tissue which interfere with the normal free motion of various parts of the body. Technics are well described and illustrations are adequate. Physical therapists and all physicians who are interested in body mechanics and posture training will find this compact little book helpful.

Laboratory Handbook for Dietetics. By M. D. Rose. Revised and rewritten by Clara Mae Taylor and Grace MacLeod. Fifth edition. Price, $5. Pp. 358, with 52 tables. The Macmillan Company, 60 5th Ave., New York 11, 1949.

This time-honored text of the late Mary Swartz Rose has been revised and rewritten. The purpose of the book has remained the same, namely, "to explain the problems involved in the calculations of food values and food requirements and the construction of dietaries, and to furnish reference tables which will minimize the labor involved in such work." However, the progress of the science of nutrition and the rapidly accumulating knowledge of the quantitative requirements of the human body and of the chemical composition of food materials have provided much new and essential information for inclusion.

The fifth edition is divided into four parts for convenience in use. Part I includes a discussion on the functions of food and food requirements for normal persons under varying conditions of age and activity. Part II deals with problems in dietary calculations. Part III carries 22 useful reference tables. Part IV gives 17 tables of food composition. Included for the first time in this handbook are tables giving essential amino acids in single proteins, mixed proteins and foods, approximate cooking losses and new vitamin and mineral values. Food values are expressed in both weights and measures, i. e., per hundred grams, per ounce, per

pound and per hundred calories. Although food values expressed per portion are included, most persons find little practical use for these recordings.

The rich amount of material incorporated in this book is well organized and easily understood. Furthermore, the subdivisions in the table of contents and the carefully prepared index contribute to ease in using the handbook. Rose's "Laboratory Handbook for Dietetics" is highly recommended to the teacher, the community and public health nutritionist, the hospital dietitian, the advanced student in nutrition, the physician and other persons who are interested in the quantitative aspects of the food supply and its nutritive value.

Tratamiento de las meningitis agudas supuradas en el niño. By S. Bonaba, A. Carrau, E. Peluffo, M. L. Saldun de Rodriguez and G. Solovey. No price given. Pp. 107, with 14 tables and diagrams. Garcia Morales-Mercant, Dante 1978, Montevideo, Uruguay, 1948.

This excellent little monograph, although written in Spanish, is easily understood and presents an excellent résumé of the authors' experience with "purulent meningitis." In this term is included Hemophilus influenzae, pneumococcic, meningococcic, streptococcic and Salmonella meningitis. The authors used the sulfonamides, penicillin and streptomycin. Their mortality from influenzal meningitis was 27.7 per cent, from pneumococcic meningitis, 27.7 per cent, from meningococcic and streptococcic meningitis none, from Salmonella meningitis (1 case) 100 per cent and from that caused by undetermined organisms 20 per cent. Considerable space is given to the use of streptomycin in meningitis, and a separate chapter is on the exclusion of intrathecal therapy. The bibliography is complete for both Spanish and American authors.

Lecciones de terapéutica infantil. Edited by Dr. Juan P. Garrahan. No price given. Pp. 468, with 20 plates and diagrams. Libreia y editorial "El Ateneo," Florida 340-Córdoba 2099, Buenos Aires, Argentina, 1949.

This book consists of a series of lectures that were part of a course in pediatrics offered by the faculty of the Institute of Pediatrics and Infant Welfare of the Hospital de Clinicas of Buenos Aires, during July 1948.

These conferences are on therapeutics, diarrheas, malnutrition, rheumatic fever, obesity, tuberculosis, vomiting, nephrosis, meningitis and the various causes of pain in the limbs of children. In an appendix other pediatricians who were not on the program offer short, well written discussions on the latest advances in the therapy of various diseases of childhood.

Inasmuch as each of the authors is a specialist in his particular field, the aim of each article is to inform others of the actual treatment that the institute is carrying on and to discuss the reasons such treatment was adopted and the results obtained. All these articles are well done and have excellent bibliographies in both the Spanish and the English literature. Dr. Garrahan opened and closed the conference with lectures emphasizing the therapeutic and human aspects of pediatrics.

Children with Mental and Physical Handicaps. By J. E. Wallace Wallin, Ph.D. Price, $6.65. Pp. 549, with 34 illustrations. Prentice-Hall, Inc., 70 5th Ave., New York 11, 1949.

Written by a psychologist who has worked for years in clinical and abnormal psychology, mental hygiene and the education and training of physically and men-

tally handicapped children, this book is intended as a reference for lay and professional workers in these fields.

The first eight chapters are concerned with mental defectiveness and present physical, psychologic, educational, sociovocational and etiologic considerations and classifications. The author's treatment of this material is often ponderous and confusing. Even the trained psychologist or physician will find himself mystified by the obvious, especially in the author's attempt to differentiate the amentias from the dementias. Chapter 2, an attempt to untangle the confusion of "Multiple Definitions of Mental Defectiveness," resembles the psychologists' maze, a verbal one with many frustrating, blind or false passages.

The balance of the twenty-one chapters presents descriptions of special clinical types or conditions which are or may be associated with mental defectiveness, with a consideration of special treatment and training problems, including those of the doubly (physically and mentally) handicapped.

Medical readers will find a number of unfortunate inaccuracies in the text; for example, in chapter 17, "The Orthopedically Disabled: Cerebral Palsy," the author lists under "Causes of Postnatal Types" tuberculosis of the bones and joints, rheumatic fever, osteomyelitis and anterior poliomyelitis, all as bacterial causes of cerebral palsy. Epidemiologists and clinicians concerned with poliomyelitis will challenge much of the material in the chapter on this disease.

Altogether, though the author has gathered and condensed much interesting material and provides a wealth of references, the inaccuracies, misinformation, biased presentations and confused editing vie to disconcert and discourage the medical reviewer.

La streptomycine et le "Pas" dans le traitement de la tuberculose chez l'enfant. By Max-Henri Béguin. Supplement to Annales pædiatrici; Jahrbuch für Kinderheilkunde, fasc. 49. Price, 8 Swiss francs. Pp. 96, with 14 illustrations. S. Karger, Holbeinstrasse 22, Basel, Switzerland, 1949.

This monograph comes from the Clinique Infantile Universitaire (Hospital Jenner), Berne, Switzerland. The author reports on 35 cases of tuberculosis in infants and children treated with streptomycin alone or with streptomycin and paraaminosalicylic acid ("aminacyl"). The patients are divided into groups according to the type of tuberculosis present. Before giving his own cases in detail, the author reviews the literature on other similar patients treated with streptomycin. In this way one arrives with him, through the experiences cited, at a considered opinion of the optimum dosage and of the best methods of administration. In the 12 patients with tuberculous meningitis, no difference in response was noted between those receiving streptomycin alone and those receiving it in association with a sulfonamide drug or paraaminosalicylic acid. All showed pronounced and prolonged amelioration of symptoms but a final fatal outcome, except in 1 child. In this patient there was complete recovery; however, tubercle bacilli had never been recovered from the child. In the other types of tuberculosis, including miliary, pericardial, peritoneal, intestinal and primary, the patients receiving paraaminosalicylic acid in addition to streptomycin seemed to make particularly favorable and rapid progress. Smaller doses of streptomycin were effective and resistance of the tubercle bacilli seemed less likely to develop.

The author also gives a historical review of antibiotics and tuberculosis. He presents sections on streptomycin and the tubercle bacillus in vitro, including the acquisition of resistance, on experimental tuberculosis treated with streptomycin and on the distribution of streptomycin in the body and methods of its administration. Following the report of cases, he reviews the toxicity of streptomycin,

the modification produced by it in anatomicopathologic lesions and presents a final section on dosage and treatment in association with other medications.

The author is thoroughly familiar with his subject. His style and arrangement of material are clear and effective. There is a full bibliography but no index.

Child Development: Physical and Psychological Growth Through the School Years. Second edition. By Marian E. Breckenridge, M.S., and E. Lee Vincent, Ph.D. Price, $4. Pp. 622, with 43 illustrations. Philadelphia: W. B. Saunders Company, 1949.

This is a revised edition of a text which first appeared in its present form and with its present purposes in 1943. The authors have been studying the growth and development of children for many years, chiefly at the Merrill-Palmer School, in Detroit. Jointly with Winifred Rand, they have published several editions of a companion volume (Growth and Development of the Young Child, fourth edition, Philadelphia, W. B. Saunders and Company, 1946). Both these volumes are broad in scope, practical in outlook and soundly rooted on studies of children.

The present revised edition of "Child Development" deals primarily with the problems of the school years, but the principal features of the growth stages of the earlier and later age periods are presented to provide continuity and, particularly, to give a picture of the more immature stages of development for recognition when they appear in children of the school years. The new edition reflects the advances of knowledge resulting from research in child development during the past five years and the intensive application of the authors to the accumulation and interpretation of this knowledge. There are 1,089 references in the bibliography, but this reflects wide coverage of subject matter rather than lack of critical selection. The constant documentation in the text provides the research background and reflects the scientific approach adopted by the authors, but the text is practical and readable and should be acceptable to all students without allowance for the content of their scientific training.

It is designed for professional students in psychology, teacher training, home economics, medicine, nursing and social work, as well as for parents. Undertaking to write a book with these broad objectives is a formidable project, but the attempt appears to be successful to the extent that students in all these fields can find profit and satisfaction from its use both as a reference text and as a general review of the whole subject of child development. The subject is treated from a broad point of view and covers many fields of research and child care. Physicians will doubtless find the chapters on the principles of development, on physical influences on growth, and on growth and use of the body, physical and motor, of less interest because of familiarity, than the chapters dealing with other influences on growth: such as emotional growth, growth of sense perceptions and judgments, development of the memory, imagination and creative activity, growth of language, thought and reasoning and social and personality development. A satisfactory, in fact rather refreshing, balance appears to have been attained in the emphasis placed on constitutional factors, or "innate growth forces," and environmental or cultural forces in leading to the infinite variety of individual differences. "Personality and social development like every type of development, is dependent upon an interplay between . . . original endowment . . . and learning experiences."

The reviewer believes that this volume will prove as useful to the physician who deals with children as to any professional worker. It will be found comprehensive, sound and reasonable in its approach and a useful adjunct to any medical library.

The Adrenal Cortex. By R. Gaunt and others. Annals of the New York Academy of Sciences, volume 50, article 6. Price, $3. Pp. 170, with 94 illustrations. New York Academy of Sciences, American Museum of Natural History, Central Park W. and 77th St., New York 24, 1949.

One of the spectacular advances in physiology can be dated from 1930, when the endocrine nature of the adrenal cortex was proved. In that year the preparation of reliable adrenal cortex extracts ended the confusion and arguments and opened up a new area for physiologic and clinical observation.

These historical aspects are the basis of Gaunt and Eversole's paper which introduces the symposium on the adrenal cortex held jointly by the New York Academy of Sciences and the New York Academy of Medicine, March 21 and 22, 1948. Taken with the 1937 Symposium at Cold Spring Harbor, N. Y., these fourteen papers might be said to record the modern history of the adrenal cortex.

Sayers and Sayers report on the effect of the administration of cortical hormone in cases in which environmental stresses, such as heat, cold and trauma, are usually associated with increased elaboration of (pituitary) adrenocortical activity. They observed a quantitative reduction in the pituitary response proportional to the amount of adrenocortical hormone administered. They postulate a mechanism which regulates the elaboration of adrenocorticotropic hormone in response to the need of tissue cells for cortical steroids. Both C_{21} oxygenated and desoxygenated steroids apparently act directly on the pituitary.

Of considerable interest is the paper by Kendall on the chemistry and partial synthesis of adrenal steroids. He presents a correlation of chemical constitution with physiologic effect for synthetic preparations with minor degrees of variation in their chemical constitution. Too much credit cannot be given the role of the organic chemist for progress in the synthesis of hormones.

Lewis and Page, using adrenalectomized rats, were able to show that both synthetic and natural 11-dehydrocorticosterone protected the experimental animals from injections of minimum lethal doses of typhoid vaccine. Using exposure to cold as an "environmental stress" for adrenalectomized rats, Dorfman also observed the synthetic sterone to have protective properties comparable to those of the adrenal extract. When glycogen deposition in the liver was used for a gage of hormonal effect in adrenalectomized rats, both Dorfman and (independently) Venning reported the synthetic sterone effective. Venning further showed that 17-hydroxy-11-dehydrocorticosterone was more active in this respect than 11-dehydrocorticosterone.

Dorfman, in the seventh paper of the symposium, discusses the bioassay of adrenocortical steroids. Of the six hormones isolated from adrenal cortex, the four which are effective on carbohydrate metabolism are characterized by oxygen atoms on carbon atom 11. He noted that glycogen deposition best meets the need for accuracy but has low sensitivity in bioassay work. Methods involving the adrenalectomized mouse, which is much more sensitive, are, however, less precise. When cold protection was used as a measure of cortical hormone activity, Dorfman found lower accuracy but the highest sensitivity. Growth, survival and electrolyte metabolism were not, in his opinion, developed to a satisfactory status for bioassay methods.

In his discussion on the adrenal cortex and metabolism, Ingle draws attention to some of the probable interrelationships of the endocrine system. He warns against interpretation in terms of exclusive functions of one organ. In the matter of protein regulation, while the cortical hormones of the C_{21} oxygenated steroids cause breakdown of lymphoid tissue and inhibit growth, he is not prepared to

accept Albright's thesis of antianabolic blocking in preference to actual catabolic action. He calls attention to the present confusion with regard to the effect of cortical hormones on the conversion of carbohydrate to fat and on the storage of fat. Confusion also is found in regard to the relation of hexokinase and cortical hormones. While 11-desoxycorticosterone appears specific for its effect on electrolyte balance and the C_{21} oxygenated steroids affect carbohydrate metabolism, there is overlapping. He warns, therefore, against too rigid thinking based on end results of cortical deficiency and expects greater elucidation from newer technics in enzyme chemistry. While isolation, identification and synthesis of active compounds have been most successful, the physiologist must continue to call attention to the functioning organism as a whole.

Greep and Deane present their studies on cytology and cytochemistry of the adrenal gland. Ascorbic acid is found in granular formation throughout the adrenal cortex. From their reaction to dyes and various agents, the ketosteroids could be identified. Identified also with lipid droplets in the glomerulosa and fasciculata, the ketosteroids were found to disappear from the latter in hypophysectomized rats. In normal as well as hypophysectomized rats, injection of desoxycorticosterone was associated with gradual loss of the lipid and ketosteroid content of the glomerulosa. In the fasciculata no effect from desoxycorticosterone was noticed, while 11-oxycorticosterone caused ketosteroid droplets to disappear. From this they suggest that the glomerulosa in the rat secretes desoxycorticosterone and regulates fluid and electrolyte balance, while the fasciculata is associated with the production of 11-oxycorticosteroids and concerns gluconeogenesis, resistance to stress and antibody production. It is, therefore, they suggest, the fasciculata which is controlled by the antipituitary.

Of interest particularly to experimental pathologists and to those concerned with oncology is the report of Woolley on the adrenal cortex and its tumors. With the considerable similarity between the mouse and man and with the availability of large numbers of mice, this animal offers much in the study of adrenal tumors. The report concerns transplantation studies with six adrenal tumors from gonadectomized mice of the *cc* strain which presented variations in the development of accessory reproductive organs. In his series the cortical tumors did not appear without gonadectomy. Administration of certain endocrine preparations was effective in preventing their appearance. Interrelation with the pituitary and adrenal gland was suggested by occasional abnormalities in the anterior lobe in the experimental animals but not in the controls.

Tracing the metabolites of the adrenal cortex, Venning and Browne report on the urinary excretion of steroids. Strenuous exercise and acute trauma, such as wounds, burns or fractures, caused an increase in the output of glycogenic corticoids. There was a more pronounced excretion in healthy, well nourished subjects than in those debilitated or malnourished. Pregnancy was associated with a rise in glycogenic corticoids, but no parallel increase in 17-ketosteroids occurred.

From the study of psychoneurotic subjects compared with normal subjects, Pincus suggests that there is a lessening of the adrenocortical response to trauma in the psychoneurotic group.

Particularly appealing to clinicians is the report by Thorn and his associates on clinical studies of Addison's disease. Reviewing experience with 158 patients with Addison's disease, the authors found tuberculosis responsible for the disease in only half the patients with adrenal insufficiency. Increasing survival and prolongation of life have been due to availability of improved substitution therapy. When 11-oxycorticosterone, as well as desoxycorticosterone, becomes available,

survival will be more assured but will entail attention to the social and mental adjustment of the patients. The authors review the various diagnostic tests and treatment procedures. Of interest to note is the contraindication for a diet low in potassium while a diet high in sodium chloride is advocated for patients being given synthetic hormone therapy. They warn against excessive sodium chloride intake for a patient under hormonal treatment, although it is of great value in the untreated patient in crisis.

The final paper of the symposium is presented by Kepler and concerns the standing controversy with regard to Cushing's disease. For those unfamiliar with the reports of Anderson, Haymaker and Albright, the paper presents a good outline of the controversy. The author does not settle the issue and leaves the reader with an understanding of Ingle's statement in an earlier paper: "In the entire field of physiology I do not know of any metabolic process which is exclusively the function of a single organ."

These collected papers will be of particular value to those engaged in research in similar lines. They do not attempt a comprehensive review of all recent investigations and many significant laboratories are not represented. Such investigators in the field as Houssay, Anderson and Evans are noticeably absent and at times neglected in the bibliographies. Clinicians will find the recent text by Hartman a more systematic one for practical use.

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1950

PUBLISHERS
AMERICAN MEDICAL ASSOCIATION
CHICAGO 10, ILL.

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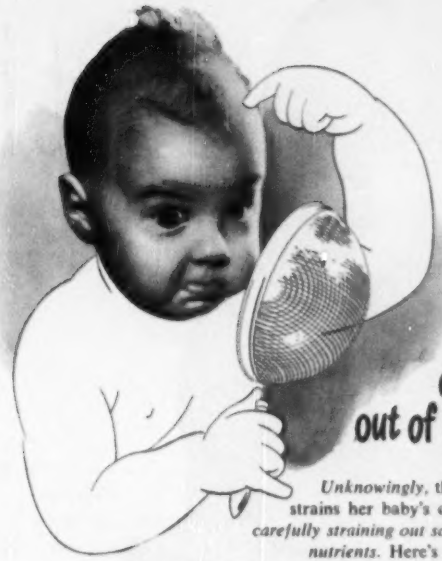

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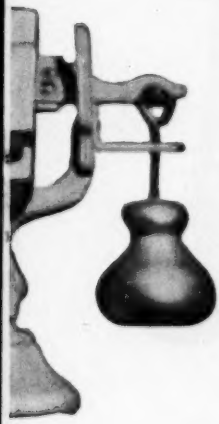

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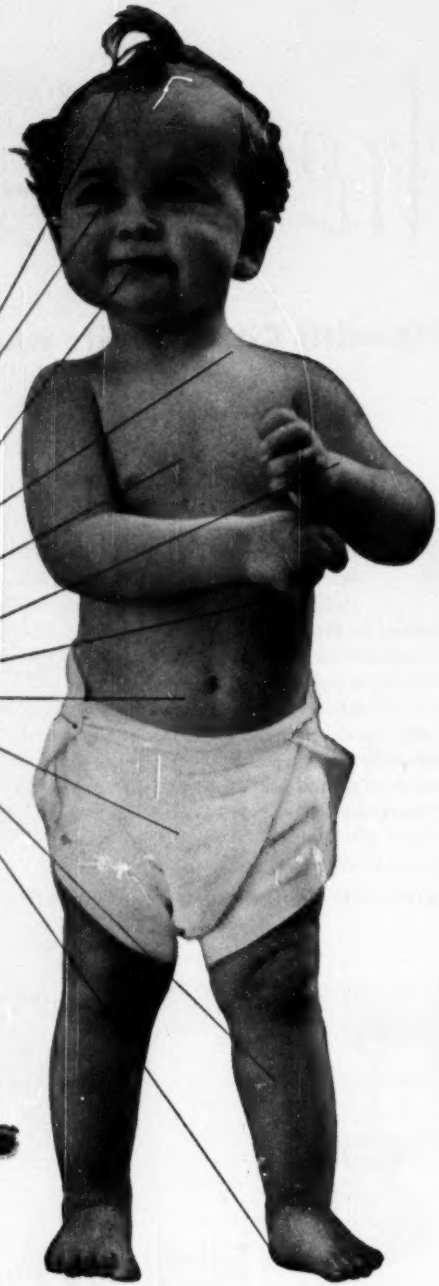

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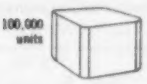

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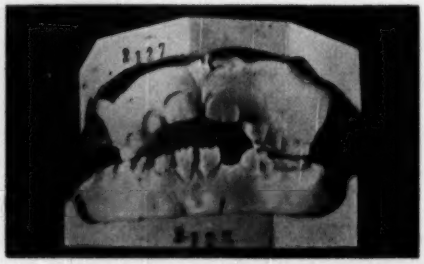

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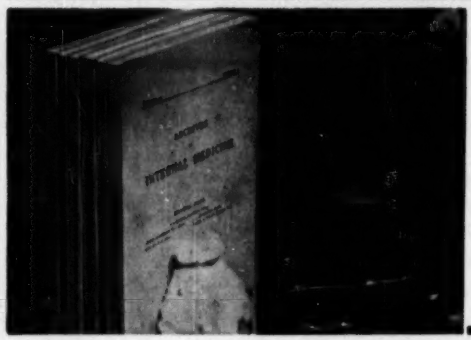

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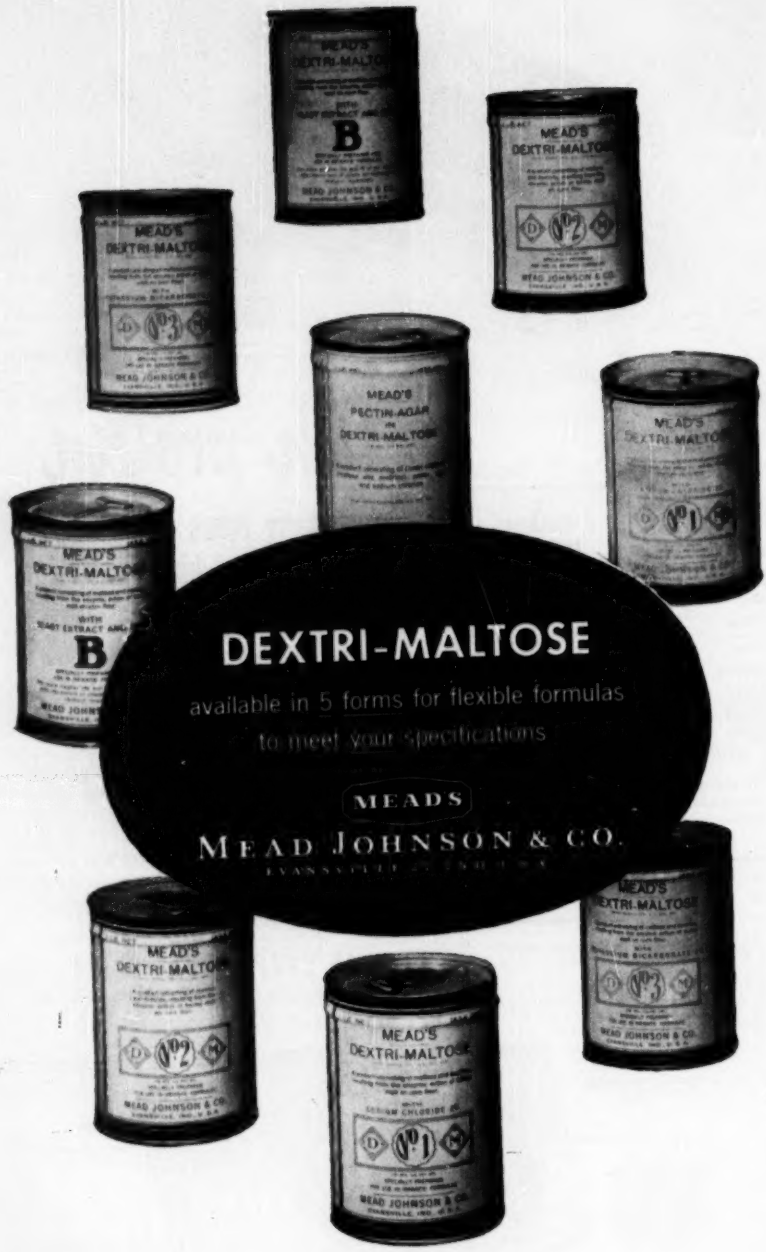
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eating milk is fun!

delicious and nutritious, too

The simple expedient of altering the form and texture of liquid milk—easily and quickly accomplished with rennet—frequently solves a number of eating problems. • Children—and oldsters, too—who (for one reason or another) tire of *drinking* milk, enjoy *eating* delicious rennet-custards. Quickly prepared, and in no way changing the nutritive values of uncooked milk, rennet-custards may be used as desserts or as between-meal snacks—varied in many ways through the availability of six different flavors and innumerable toppings. • Remember rennet next time you have a milk problem!

"JUNKET" is the trade-mark of Chr. Hansen's Laboratory, Inc. for its rennet and other food products and is registered in U.S. Patent Office.

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"Junket" Rennet Powder —sweetened, six flavors.

"Junket" Rennet Tablets —unsweetened, unflavored (particularly for very young infants and diabetics).

Throughout the *formative* years . . .

From birth to at least the age of 14 years, investigators now agree children are susceptible to rickets, with scarcely diminished frequency.[1]

The critical periods of active skeletal growth are found in infancy and childhood, lasting through at least the years just preceding puberty.[2]

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1. Follis, R. H., Jackson, D., Eliot, M. M., and Park, E. A.: *Am. Jour. Dis. Child.*, 66:1, July, 1943.
2. Stearns, G.: *Jour. Lancet*, 63:344, Nov., 1943.

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